Draft Comparative Effectiveness Review

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Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Hypertension

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

Acknowledgments

[Will be included in final report]

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[Will be included in final report]

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Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at
www.effectivehealthcare.ahrq.gov/reports/final.cfm

Background

More than 65 million American adults – approximately one-third – have hypertension. The prevalence of hypertension increases with advancing age such that more than half of people 60 to 69 years of age and approximately three-fourths of those 70 years of age and older are affected. In addition be being the number one attributable risk factor for death throughout the world, hypertension results in substantial morbidity due to its impact on numerous target organs including the brain, eyes, heart, arteries, and kidneys.

Despite the high morbidity and mortality attributable to hypertension, control remains suboptimal. In addition to several effective non-pharmacological interventions – including diet, exercise, and control of body weight – many individuals will require antihypertensive medication to lower blood pressure.

Among the many choices in antihypertensive therapy, many of the most common are those aimed at affecting the renin-angiotensin-aldosterone (renin) system. The renin system is an important mediator of blood volume, arterial pressure, and cardiac and vascular function. Components of this system can be identified in many tissues. The primary site of renin release is the kidney. The system can be triggered by sympathetic stimulation, renal artery hypotension, and decreased sodium delivery to the distal tubule. Via proteolytic cleavage, renin acts on the decapeptide substrate angiotensinogen I to the octapeptide angiotensin II. Angiotensin II acts directly on the resistance vessels to increase systemic vascular resistance and arterial pressure; stimulates the adrenal cortex to release aldosterone, leading to increased sodium and water

reabsorption and potassium excretion; promotes secretion of antidiuretic hormone, leading to fluid retention; stimulates thirst; promotes adrenergic function; and increases cardiac and vascular hypertrophy.

Therapies aimed at modifying the renin system have been used extensively for treatment of hypertension, heart failure, myocardial infarction (MI), diabetes, and renal disease.[1,2] Currently, therapies fall into one of two classes of angiotensin antagonists: the angiotensin-converting enzyme inhibitors (ACEIs), and the angiotensin II receptor antagonists (ARBs or angiotensin receptor blockers). ACEIs block conversion of angiotensin I to angiotensin II. ARBs selectively inhibit angiotensin II from activating the angiotensin specific receptor (AT_1).

While ACEIs and ARBs both target the renin system and are regarded by clinicians as effectively equivalent, it is not clear that this is appropriate. ACEIs, for example, do not entirely block production of angiotensin II due to the presence of unaffected converting enzymes. Also, ACEIs are associated with well-known adverse events not shared by ARBs, including cough (estimated incidence 5 to 20 percent) and angioedema (estimated incidence 0.1 to 0.2 percent, with a lesser reported risk with ARBs). It would be clinically useful to have a clear understanding of the state of the science with regard to the relative effectiveness of ACEIs and ARBs.

This review summarizes the evidence on the comparative long-term benefits and harms of ACEIs versus ARBs, focusing on their use for treating essential hypertension in adults. Key questions addressed are:

Key Question 1. For adult patients* with essential hypertension, how do ACEIs and ARBs† differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes‡?

*"Adult patients" are defined as adults, age 18 years or older.

†ACEIs evaluated are: Benazepril (Lotensin®), captopril (Capoten®), enalapril (Vasotec®), fosinopril (Monopril®), lisinopril (Prinivil®, Zestril®), moexipril (Univasc®), perindopril (Aceon®), quinapril (Accupril®), ramipril (Altace®), and trandolapril (Mavik®). ARBs considered are: Candesartan cilexetil (Atacand®), eprosartan (Teveten®), irbesartan (Avapro®), losartan (Cozaar®), olmesartan medoxomil (Benicar®), telmisartan (Micardis®), and valsartan (Diovan®).

‡Outcomes considered include:

Intermediate outcomes: Blood pressure control; rate of use of a single antihypertensive agent for blood pressure control; lipid levels; progression to type 2 diabetes; markers of carbohydrate metabolism/diabetes control; measures of left ventricular (LV) mass/function; and measures of kidney disease.

Health outcomes: Mortality (all-cause mortality, cardiovascular disease-specific mortality, and cerebrovascular disease-specific mortality); and morbidity (cardiac

events [myocardial infarction], heart failure, cerebral vascular disease or events [including stroke], symptomatic coronary artery disease, end-stage renal disease, peripheral vascular disease, and quality of life).

Key Question 2. For adult patients with essential hypertension, how do ACEIs and ARBs differ in safety[§], adverse events[‖], tolerability, persistence, and adherence?

[§]Safety outcomes: Overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, and switch rates.

[‖]Specific adverse events: These included, but were no limited to, weight gain, impaired renal function, angioedema, and cough.

Key Question 3. Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?

Conclusions

ACEIs and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. This conclusion is based on evidence of generally moderate quality from 49 studies (45 RCTs, two non-randomized controlled clinical trials, and one retrospective cohort and case-control study) with a total of 16,347 patients followed for periods from 12 weeks to 3.3 years (median 16 weeks).

Due to insufficient numbers of deaths or major cardiovascular events in the included studies, it is not possible to discern any differential effect of ACEIs versus ARBs for these critical outcomes. In eight studies that reported mortality, MI, or clinical stroke as outcomes, six deaths and one stroke were reported. This may reflect low event rates among otherwise healthy patients and relatively few studies with extended followup. Similarly, no differences were found in measures of general quality of life; this is based four studies, two of which did not provide quantitative data.

There was a minimally higher rate of treatment success based on use of a single antihypertensive for ARBs compared to ACEIs (approximately 1 fewer patients per 100 treated with ARBs will require more than a single agent, number-needed-to-treat [NNT]). The advantage of ARBs for this outcome was heavily influenced by retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients, or RCTs with very loosely defined protocols for medication titration and switching.

ACEIs have been consistently shown to be associated with greater risk of cough than ARBs (pooled odds ratio = 0.34). For clinical trials, this translates to a difference in rates cough of 5.7 percent ((NNT = 18); however, for cohort studies with lower rates of cough, this translates to a difference of 1.3 percent (NNT = 76). This is consistent with evidence reviewed regarding withdrawals due to adverse events, in which the NNT is on the order of 64 – that is, one more

withdrawal per 64 patients treated with an ACEI versus an ARB. There was no evidence of differences in rates of other specific adverse events.

There were no consistent differential effects of ACEIs versus ARBs on several potentially important clinical outcomes including lipid levels, progression to type 2 diabetes mellitus, markers of carbohydrate metabolism/diabetes control, left ventricular mass or function, or progression of renal disease (either based on creatinine, glomerular filtration rate, or proteinuria). While based on studies of at least moderate quality, relatively few studies assessed these outcomes over the long term.

Remaining Issues

Despite the relative importance of both ACEIs and ARBs for treatment of essential hypertension, there is a paucity of comparative evidence for long-term benefits and harms for these two classes of agents. In particular, there was a paucity of information about death or major cardiovascular events, and inconsistently reported data on adverse events. Only 13 studies compared ACEIs and ARBs for periods exceeding 1 year.

Future Research

The hypothesis that ACEIs and ARBs have clinically meaningful differences in long-term outcomes in individuals with essential hypertension is not strongly supported by the available evidence. Further research in this area should consider:

- Subgroups of special importance such as individuals with essential hypertension and diabetes mellitus, congestive heart failure, chronic kidney disease, and dyslipidemia.
- Pragmatic designs such as clinical trials in which treatment is consistent with typical clinical practice, or randomization by organizationally meaningful clusters, such as practice organizations or health plans.
- Outcomes over several years.
- Outcomes measured according to current clinical standards.
- Broader representation of groups such as the elderly and ethnic and racial minorities.

Given the demonstrated higher incidence of cough with ACEIs, it would be valuable to gain more precise understanding of the impact of cough on quality of life, care patterns (e.g., use of therapeutic agents for cough symptoms or conditions associated with cough), and health outcomes, particularly for individuals who continue to use ACEIs.

Introduction

Background

More than 65 million American adults (one-third) have hypertension. The prevalence of hypertension increases with advancing age such that more than half of people 60 to 69 years of age and approximately three-fourths of those 70 years of age and older are affected.[3] Furthermore, increasing prevalence of obesity may further increase the prevalence of hypertension in the United States. According to estimates from the World Health Organization, worldwide prevalence estimates for hypertension may be as much as 1 billion individuals, and suboptimal BP is the number one attributable risk factor for death throughout the world.[4] Substantial excess morbidity also occurs when hypertension affects numerous target organs including the brain, eyes, heart, arteries, and kidneys.

Despite the high morbidity and mortality attributable to hypertension, control remains suboptimal. Approximately one-third of adults remain unaware of their hypertension, over 40 percent of individuals with hypertension are not on treatment, and two-thirds of hypertensive patients continue to have blood pressures above even modest treatment goals (< 140/90 mmHg).[5] Several non-pharmacological interventions – including diet, exercise, and control of body weight – are effective in lowering blood pressure; however, such therapies are often insufficient or not sustained, resulting in a reliance on pharmacotherapy. Various classes of antihypertensive drug treatments are available to manage hypertension, but determining the comparative effectiveness of antihypertensives is complicated. Therapeutic choices may be influenced by patient characteristics – including comorbidities and race – that also affect the risk of certain clinical end points. Multi-drug therapy is often required to achieve satisfactory control, leading to greater variables to consider in treatment choices.[5] Finally, adverse events that are characteristic of the individual agents or drug classes further complicate therapeutic decisionmaking.

The renin-angiotensin-aldosterone (renin) system is an important mediator of blood volume, arterial pressure, and cardiac and vascular function. Components of this system can be identified in many tissues. The primary site of renin release is the kidney. The system can be triggered by sympathetic stimulation, renal artery hypotension, and decreased sodium delivery to the distal tubule. Via proteolytic cleavage, renin acts on the decapeptide substrate angiotensinogen I to the octapeptide angiotensin II. Angiotensin II acts directly on the resistance vessels to increase systemic vascular resistance and arterial pressure; stimulates the adrenal cortex to release aldosterone, leading to increased sodium and water reabsorption and potassium excretion; promotes secretion of antidiuretic hormone, leading to fluid retention; stimulates thirst; promotes adrenergic function; and increases cardiac and vascular hypertrophy.

Therapies aimed at modifying the renin system have been used extensively for treatment of hypertension, heart failure, myocardial infarction (MI), diabetes, and renal disease.[1,2] Currently, therapies fall into one of two classes of angiotensin antagonists: the angiotensin-converting enzyme inhibitors (ACEIs), and the angiotensin II receptor antagonists (ARBs or angiotensin receptor blockers). ACEIs block conversion of angiotensin I to angiotensin II. ARBs selectively inhibit angiotensin II from activating the angiotensin specific receptor (AT_1).

While ACEIs and ARBs both target the renin system and are regarded by clinicians as effectively equivalent, it is not clear that this is appropriate. ACEIs, for example, do not entirely block production of angiotensin II due to the presence of unaffected converting enzymes. Also, ACEIs are associated with well-known adverse events not shared by ARBs, including cough (estimated incidence 5 to 20 percent) and angioedema (estimated incidence 0.1 to 0.2 percent, with a lesser reported risk with ARBs). Further, distinguishing effectiveness between these two groups of commonly used angiotensin antagonists is particularly problematic. Although both ACEIs and ARBs are highly effective in lowering blood pressure among patients with essential hypertension,[1,2] the comparative effectiveness of the ACEIs and ARBs is not known. In addition, because many patients with hypertension require multiple medications to achieve adequate blood pressure control, angiotensin antagonists are often optimal second-line antihypertensive drugs. However, the relative advantages and disadvantages of ACEIs versus ARBs are not well known despite several studies that have compared the effectiveness within other classes of antihypertensive drugs as well as recent drug class reviews for ACEIs[1] and ARBs.[2]

In this comparative effectiveness review, we examine the scientific literature on ACEIs and ARBs for individuals with hypertension regarding their relative benefits (blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes), as well as relative risks (safety, adverse events, tolerability, persistence, and adherence). In addition, we will examine the clinical determinants of these outcomes with a focus on the long-term impact.

Scope and Key Questions

This review summarizes the evidence on the comparative long-term benefits and harms of ACEIs versus ARBs for treating essential hypertension in adults. Key questions addressed are:

Key Question 1. For adult patients* with essential hypertension, how do ACEIs (angiotensin-converting enzyme inhibitors) and ARBs (angiotensin II receptor antagonists)† differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes‡?

*"Adult patients" are defined as adults, age 18 years or older.

†Table 1 lists the specific ACEIs and ARBs evaluated in this review and describes their characteristics and current indications.

‡Outcomes considered include:

Intermediate outcomes: Blood pressure control; rate of use of a single antihypertensive agent for blood pressure control; lipid levels; progression to type 2 diabetes; markers of carbohydrate

metabolism/diabetes control; measures of left ventricular (LV) mass/function; and measures of kidney disease.

Health outcomes: Mortality (all-cause mortality, cardiovascular disease-specific mortality, and cerebrovascular disease-specific mortality); and morbidity (cardiac events [myocardial infarction], heart failure, cerebral vascular disease or events [including stroke], symptomatic coronary artery disease, end-stage renal disease, peripheral vascular disease, and quality of life).

Key Question 2. For adult patients with essential hypertension, how do ACEIs and ARBs differ in safety[§], adverse events[‖], tolerability, persistence, and adherence?

[§]Safety outcomes: Overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, and switch rates. (For practical reasons, we separate safety/adverse events and tolerability/persistence (including switch rates), as the latter may or may not be due to identifiable adverse events.)

[‖]Specific adverse events: These included, but were no limited to, cough and angioedema.

Key Question 3. Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?

456 **Table 1. Characteristics and labeled indications of ACEIs and ARBs evaluated in this report**
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Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
ACEIs				
Benazepril (Lotensin®)	- After oral administration, peak plasma concentrations reached within 0.5-1 hr. - Effective half-life in adults following multiple dosing 10-12 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	Treatment of hypertension. May be used alone or in combination with thiazide diuretics.	Initial dose for adults not receiving a diuretic is 10 mg once daily. Usual maintenance range is 20-40 mg per day in a single or two equal doses.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - In patients with renal insufficiency (creatinine clearance ≤30 mL/min/1.73 m²) peak levels and initial half-life increase, time to steady state may be delayed. Recommended initial dose in such patients is 5 mg once daily. Dosage may be titrated upward until BP is controlled or to a maximum total daily dose of 40 mg.
Captopril (Capoten®)	- After oral administration, peak plasma concentrations reached in 1 hr. Presence of food reduces absorption by 30-40%. - In adults, effective half-life < 3 hr (accurate determination of half-life not possible). - In a 24-hr period, 95% of observed dose eliminated in the urine. - Reduction of BP maximum at 60-90 minutes after oral administration, duration of effect dose-related. - Reduction in BP may be progressive.	1. Treatment of hypertension. 2. Treatment of congestive heart failure. 3. To improve survival following MI in clinically stable patients.	Should be taken 1 hr before meals, dosage must be individualized. Initial dose is 25 mg twice per day or three times per day. Dosage may be increased to 50 mg twice per day or three times per day. Usual dose range is 25-150 mg twice per day or three times per day.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment: initial daily dose should be reduced, smaller increments should be utilized for titration, and minimal effective dose should be calculated.
Enalapril (Vasotec®)	- After oral administration, peak serum concentrations occur within 1 hr. - Primarily renal, 94% of dose is recovered in the urine and feces. - Effective half-life following	Treatment of hypertension.	10-40 mg per day in a single or two divided doses. Daily dose should not exceed 50 mg. Dosage reduction and/or discontinuation may be required for some patients who develop increases in blood urea and serum creatinine.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. Enalapril has been detected in human breast milk. - Dose selection for elderly patients should be cautious, usually starting

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
	multiple doses is 11 hr. - With GFR ≤ 30 mL/min, time to peak concentration and steady state delayed.			at the low end of the dosing range.
Fosinopril (Monopril®)	- After oral administration, peak concentrations achieved in 3 hr. - Terminal elimination half-life is 12 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or with thiazide diuretics. 2. For heart failure as adjunctive therapy when added to conventional therapy, including diuretics with or without digitalis.	Initial dosage is 10 mg once daily, both as monotherapy and when the drug is added to a diuretic.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - In children, doses between 0.1 and 0.6 mg/kg. For children weighing more then 50 kg, dosage is 5-10 mg once daily. - For heart failure patients, an initial dose of 5 mg can be increased over a several-week period but not exceeding 40 mg once daily.
Lisinopril (Prinivil®; Zestril®)	- Reaches peak serum concentrations within 7 hr. - On multiple doses, effective half-life accumulation is 12 hr. - Excreted primarily through the kidneys.	1. Treatment of hypertension. 2. As adjunctive therapy in the management of heart failure not responding to diuretics and digitalis. 3. Acute MI – for the treatment of hemodynamically stable patients, to improve survival.	Initial dose is 10 mg once daily, usual dose range 20-40 mg daily in a single dose. Patients on a diuretic dosage should be adjusted according to BP response, and the diuretic should ideally be discontinued. For patients with creatinine clearance ≤ 10 mL/min, recommended initial dose is 2.5 mg, can be titrated upward up to a maximum of 40 mg daily.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Dose selection for elderly patients should start at the low end of dosing range.
Moexipril (Univasc®)	- Bioavailability of oral drug is 13% compared to IV; markedly affected by food. - After oral administration, 7% appears in urine (vs. 40% of IV dose), 52% in feces (vs. 20% of IV dose).	Treatment of hypertension.	Initial dose in patients not receiving diuretics is 7.5 mg 1 hr prior to meals, once daily. Recommended dose range is 7.5-30 mg daily in one or two divided doses. Diuretic therapy should ideally be discontinued or an initial dose of 3.75 mg should be used with medical supervision. For patients with creatinine clearance ≤ 40 mL/min/1.73 m^2, the recommended initial dose is 3.75 mg once daily, can be titrated to a maximum daily dose of 15 mg.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Dosage should be adjusted for populations with decreased renal function, mild to moderate cirrhosis and in elderly patients.

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Perindopril (Aceon®)	- After oral administration, peak plasma concentrations occur at approximately 1 hr. - Mean half-life 0.8-1.0 hr. - Clearance almost exclusively renal.	1. Treatment of hypertension. May be used alone or in combination with thiazide diuretics. 2. Stable coronary artery disease: to reduce risk of cardiovascular mortality or non-fatal MI.	Initial dose is 4 mg once daily. May be titrated upward until BP is controlled to a maximum of 16 mg per day. Usual dose range is 4-8 mg as single daily dose. May be given in two divided doses.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Dose selection for elderly patients should start at the low end of dosing range. - Patients with renal impairment: initial daily dose should be reduced.
Quinapril (Accupril®)	- After oral administration, peak plasma concentrations reached within 1 hr. - After multiple oral dosing, effective half-life within 2 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or with thiazide diuretics. 2. Management of heart failure as adjunctive therapy when added to conventional therapy, including diuretics and/or digitalis.	Initial dosage for patients not on diuretics is 10-20 mg once daily. Dosage adjusted according to BP measured at peak and trough.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment and heart failure: initial daily dose should be reduced. - Recommended dosage for elderly patients is 10 mg once daily followed by titration to the optimal response.
Ramipril (Altace®)	- After oral administration, peak plasma concentrations reached within 1 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or in combination with thiazide diuretics. 2. Reduction in risk of MI, stroke, and death from cardiovascular causes for patients 55 years or older at high cardiovascular risk.	Initial dose for patients not receiving a diuretic is 2.5 mg once daily. Dosage adjustment according to BP response. Usual maintenance dosage is 2.5-20 mg once daily in a single dose or divided equally into 2 doses.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment: initial daily dose should be reduced, smaller increments should be utilized for titration and minimal effective dose should be calculated.
Trandolapril (Mavik®)	- After oral administration under fasting conditions, peak concentrations occur within 1 hr. - Effective half-life approximately 6 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or with other antihypertensive medication. 2. Heart failure post-MI or LV dysfunction post-MI. Used to decrease risk of death and heart failure-related hospitalization.	Initial dosage in patients not receiving a diuretic is 1 mg once daily in non-black patients and 2 mg in black patients. Dosage adjusted according to BP.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment: initial daily dose should be reduced, smaller increments should be utilized for titration and minimal effective dose should be calculated.
ARBs				
Candesartan cilexetil (Atacand®)	After oral administration, peak serum concentrations reached after 3-4 hr.	1. Treatment of hypertension. May be used alone or in combination with other	Initial dose is 16 mg once daily. Can be given once or twice daily with doses ranging from 8-32 mg. Effect	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
	- Elimination of half-life occurs within 9 hr. - Excreted in urine and feces.	antihypertensive agents. 2. Heart failure: used in patients with LV systolic dysfunction to reduce risk of death and heart failure.	is usually present within 2 weeks, and maximal BP reduction occurs within 4-6 weeks.	the developing fetus. - Lower dose for patients with moderate hepatic impairment or depletion of intravascular volume.
Eprosartan (Teveten®)	- After oral administration, plasma concentrations peak around 1-2 hr in the fasted state. - Mean terminal elimination half-life following multiple doses of 600 mg was 20 hr. - Eliminated primarily by biliary and renal excretion.	Treatment of hypertension. May be used alone or in combination with other antihypertensives, such as diuretics and calcium channel blockers.	Initial dose is 600 mg once daily. Can be given once or twice daily with doses ranging 400 mg to 800 mg.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Elderly, hepatically impaired, or renally impaired patients should not exceed 600 mg daily.
Irbesartan (Avapro®)	- After oral administration, peak plasma concentrations reached at 1.5-2 hr. - Average terminal elimination of half-life is 11-15 hr. - Eliminated primarily by biliary and renal excretion.	1. Treatment of hypertension. May be used alone or with other antihypertensive agents. 2. Nephropathy in type 2 diabetic patients. Indicated for treatment of patients with an elevated serum creatinine and proteinuria > 300 mg/day). Reduces rate of progression of nephropathy.	Initial dose is 150 mg once daily. Patients who require more reduction in BP should be titrated to 300 mg once daily.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Nephropathy in type 2 diabetic patients: maintenance dose is 300 mg once daily. - Children (6-12 years): initial dose of 75 mg, up to 150 mg once daily. Ages 13-16: initial 150 mg once daily, can be titrated to 300 mg once daily, higher doses not recommended. - Lower initial dose for patients with depletion of intravascular volume or salt.
Losartan (Cozaar®)	- After oral administration, mean peak concentrations reached in 1 hr. - Terminal half-life is 2 hr. - Eliminated primarily by biliary and renal excretion.	1. Treatment of hypertension. May be used alone or with other antihypertensive agents, including diuretics. 2. Hypertensive patients with LV hypertrophy: reduces risk of stroke, though some evidence that this does not apply to black patients. 3. Nephropathy in type 2	Initial dose is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume and patients with history of hepatic impairment. May be given twice daily with total doses from 25 mg to 100 mg.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Pediatric hypertensive patients (6 years and greater): starting dose is 0.7 mg/kg once daily (up to 50 mg total) given as tablet or a suspension.

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
		diabetic patients: reduces rate of progression of nephropathy as measured by doubling of serum creatinine or end-stage renal disease.		- Hypertensive patients with LV hypertrophy: starting dose is 50 mg once daily. Based on BP response, hydrochlorothiazide 12.5 mg daily should be added and/or dose of losartan should be increased to 100 mg once daily followed by an increase of hydrochlorothiazide to 25 mg once daily.
Olmesartan medoxomil (Benicar®)	- After oral administration, peak plasma concentrations reached after 1-2 hr. - Terminal elimination of half-life is 13 hr. - Eliminated primarily by biliary and renal excretion.	Treatment of hypertension. May be used alone or with other antihypertensive agents.	Initial dose is 20 mg once daily. For patients requiring further reduction in BP, dose may be increased to 40 mg.	When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - In patients with impaired renal failure, a lower starting dose should be considered.
Telmisartan (Micardis®)	- After oral administration, peak concentrations reached within 0.5-1 hr. - Terminal elimination of half-life is 24 hr. - Eliminated mostly through feces.	Treatment of hypertension. May be used alone or with other antihypertensive agents.	Starting dose is 40 mg once daily. BP response is dose-related over range of 20-80 mg.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Patients with depletion of intravascular volume, biliary obstructive disorders, or hepatic insufficiency should start treatment under close medical supervision.
Valsartan (Diovan®)	- After oral administration, peak plasma concentrations reached within 2-4 hr. - Average elimination half-life about 6 hr. - Primarily eliminated in feces and urine.	1. Treatment of hypertension. May be used alone or with other antihypertensive agents. 2. Heart failure: used in treatment of heart failure, reduces hospitalizations. 3. Post-MI: used to reduce cardiovascular mortality.	Initial dose is 80 mg or 160 mg once daily in patients who are not volume depleted. May be used over a dose range of 80 mg to 320 mg once daily.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Care should be given when dosing patients with hepatic or severe renal impairment.

Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor antagonist(s); BP = blood pressure; GFR = glomerular filtration rate; hr = hour(s); LV = left ventricular; MI = myocardial infarction

Methods

Topic Development

The topic for this report was nominated in a public process. With input from technical experts, the Scientific Resource Center (SRC) for the AHRQ Effective Health Care Program drafted the initial key questions and, after approval from AHRQ, posted them to a public Web site. The public was invited to comment on these questions. After reviewing the public commentary, the SRC drafted final key questions and submitted them to AHRQ for approval.

Search Strategy

We conducted a comprehensive search of the scientific literature to identify systematic reviews, randomized controlled trials, and non-randomized comparative studies relevant to the key questions. Searches of electronic databases used the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. Searches included terms for drug interventions, hypertension, and study design, and were limited to studies published in English after 1988. The texts of the major search strategies are given in Appendix A. We also reviewed selected materials received from the SRC and the reference lists of relevant review articles. We did not undertake a systematic search for unpublished data.

To identify literature describing direct comparisons of ACEIs versus ARBs we searched:

- MEDLINE® (1966 to May Week 3 2006).
- The Cochrane Central Register of Controlled Trials.
- A register of systematic reviews underway in the Cochrane Hypertension Review Group.
- Scientific information packets submitted through the SRC by AstraZeneca, Bristol-Myers Squibb, Kos, and Merck.

We conducted additional searches in MEDLINE® for studies of ARBs versus other (non-ACEI) comparators and ACEIs versus other (non-ARB) comparators for potential use in the event that evidence from direct head-to-head trials proved to be insufficient for some or all of the outcomes of interest in this review. The search strategies used to identify this potentially relevant indirect comparator literature are included in Appendix A. The process used to screen this literature and evaluate its relevance is described in Appendix B.

Our searches identified a total of 1182 citations. We imported all citations into an electronic database (ProCite® 4).

Study Selection

We developed criteria for inclusion and exclusion based on the patient populations, interventions, and outcome measures specified in the key questions. The abstract screening criteria we used (Appendix C) were designed to identify potentially relevant indirect comparator studies (ACEI

versus non-ARB or placebo and ARB versus non-ACEI or placebo), as well as direct head-to-head comparator studies. We retrieved the full text of all potentially relevant abstracts for further review. In the case of direct comparator studies, we applied a second, more stringent set of criteria for inclusion and exclusion (Appendix C). Full-text screening of the indirect comparative literature proceeded along a separate track, which is described in Appendix B.

The remainder of this section describes in greater detail the criteria we used to screen the direct comparator literature.

Population and Condition of Interest

As specified in the key questions, this review focused on adult patients (age 18 years or older) with essential hypertension, as defined by study authors. We included studies with patients of mixed ages and mixed diagnoses only if results were reported separately for the relevant subgroups.

Interventions and Comparators of Interest

We included the ACEIs and ARBs listed in Table 1. In addition to straightforward comparisons of a single ACEI versus a single ARB, we also included "grouped" comparisons (e.g., a specific ARB versus "ACEIs" or unspecified "ARBs" versus unspecified "ACEIs") and comparisons of an ACEI + drug X versus an ARB + drug X (e.g., losartan + hydrochlorothiazide [HCTZ] versus enalapril + HCTZ). We excluded comparisons of an ACEI + drug X versus an ARB + drug Y (e.g., enalapril + manidipine vs. irbesartan + HCTZ).

Studies with treatment protocols that permitted the addition of other antihypertensive medications during the trial if certain blood pressure targets were not met were included provided the co-intervention protocols were the same in both groups.

Outcomes of Interest

We considered a wide range of outcomes pertaining to the long-term benefits and harms of ACEIs versus ARBs. These are listed above in the section on "Scope and Key Questions." In somewhat greater detail, and in order of relative priority, these outcomes were:

- Blood pressure control (we preferred seated trough blood pressure, where reported).
- Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific).
- Morbidity (especially major cardiovascular events [MI, stroke] and measures of quality of life).
- Safety (focusing on serious adverse event rates, overall adverse event rates, and withdrawals due to adverse events).
- Specific adverse events (including, but not limited to, cough and angioedema).
- Persistence/adherence.
- Rate of use of a single antihypertensive for blood pressure control.
- Other intermediate outcomes:

- Lipid levels (high-density lipoprotein [HDL], low-density lipoprotein [LDL], total cholesterol [TC], and triglyceride [TG]).
- Rates of progression to type 2 diabetes.
- Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], insulin or other diabetes medication dosage, fasting plasma glucose, or aggregated measures of serial glucose measurements).
- Measures of LV mass/function (left ventricular mass index [LVMI] and ejection fraction [LVEF]).
- Measures of kidney disease (creatinine/glomerular filtration rate [GFR], proteinuria).

The key questions ask about the comparative *long-term* benefits and harms of ACEIs versus ARBs for treating hypertension, but do not define precisely what is meant by "long-term." We initially interpreted this to mean 6 months or longer, but decided after the abstract screening to reduce this to 12 weeks or longer to capture more studies. We regard this as a generous interpretation of "long-term" and expect that any insights that might be gained about long-term benefits and harms from studies < 12 weeks will also emerge from the pool of longer studies.

Types of Studies

We included comparative clinical studies of any design, including randomized controlled trials (RCTs), non-randomized controlled clinical trials, retrospective and prospective cohort studies, and case-control studies.

We excluded studies with fewer than 20 total patients in the ACEI and ARB treatment arms.

Data Extraction

We developed a data abstraction form/evidence table template for abstracting data from the included studies (Appendix D) and used the same form for all study designs and to capture data relevant to all three key questions. Abstractors worked in pairs: the first abstracted the data, and the second over-read the article and the accompanying abstraction to check for accuracy and completeness. The completed evidence table is provided in Appendix E.

We extracted the following data from included trials: geographical location; funding source; study design; interventions (including dose, duration, dose titration protocol [if any], and co-interventions [if any]); population characteristics (including age, sex, race/ethnicity, baseline blood pressure, concurrent medications, and comorbidities); recruitment setting; inclusion and exclusion criteria; numbers screened, eligible, enrolled, and lost to followup; and results for each outcome.

Quality Assessment

We used predefined criteria to assess the quality of individual controlled trials and prospective or retrospective observational (cohort) studies. To assess the quality of clinical trials and cohort studies, we adapted criteria developed by the U.S. Preventive Services Task Force (USPSTF) and the CRD.[6,7]

Studies were graded as "good," "fair," or "poor" in quality according to the following definitions:

> A "good" study has the least bias and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
>
> A "fair" study is susceptible to some bias, but probably not sufficient to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are *possibly* valid, while others are *probably* valid.
>
> A "poor" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

If a study was rated as fair or poor, assessors were instructed to note important limitations on internal validity based on the USPSTF/CRD criteria, as adapted here:

1) Initial assembly of comparable groups:
   - For RCTs: Adequate randomization, including concealment and whether potential confounders were distributed equally among groups.
   - For cohort studies: Consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.

2) Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination).

3) Important differential loss to followup or overall high loss to followup.

4) Measurements: Equal, reliable, and valid (includes masking of outcome assessment).

5) Clear definition of interventions.

6) All important outcomes considered.

7) Analysis: Adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs.

Assessment of each study's quality was made by a single rater and then evaluated by a second rater. Finally, quality assessments were reviewed across studies. Disagreements were resolved by consensus.

Applicability

We did not provide a global rating of applicability (such as "high" or "low") because applicability may differ substantially based on the user of this report. However, applicability of research studies was assessed by noting the most important *potential* limitations in a study's applicability from among the list described by Rothwell.[8] These criteria, slightly adapted by the SRC, are reproduced in Appendix F. Assessors were instructed to list the most important (up to three) limitations affecting applicability, if any, based on this list.

Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer followup periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the spectrum of patients that will use a drug, have a test, or undergo a procedure than results from highly selected populations in efficacy studies.

Rating the Body of Evidence

We addressed the body of evidence for each key question using the GRADE framework.[9] In rating the strength of a body of evidence we considered the number of studies, the size of the studies, strength of study design, and the quality of individual studies. In addition, as part of the GRADE framework we assessed the consistency across studies of the same design, consistency across different study designs, the magnitude of effect, and applicability. Finally, if applicable, we considered the likelihood of publication bias and (for observational studies especially) the potential influence of plausible confounders. We commented specifically if it is difficult or impossible to assessing certain of these dimensions.

Data Synthesis

We considered together all studies comparing ACEIs and ARBs for a given outcome. We evaluated similarities in terms of specific drugs within these classes, study populations, potential confounders, and duration of followup. Given that many studies did not have the statistical power to determine equivalence for the outcomes relevant to this review (often not the primary outcomes evaluated by study investigators), we considered pooling in an attempt to overcome the type II error.

Studies related to a specific outcome were candidates for a quantitative synthesis when we were able to identify at least four clinically similar studies of the same outcome. Regardless of the presence of heterogeneity, we stratified analyses by study design, separating RCTs from observational studies. In the absence of heterogeneity, a summary effect size was calculated in order to more precisely estimate the confidence limits for an overall effect. We used Comprehensive Meta-analysis version 2 (Borenstein M, Hedges L, Higgins J, Rothstein H.

Comprehensive Meta-analysis Version 2, Biostat, Englewood NJ [2005]) to test for heterogeneity and for pooling. In the presence of heterogeneity, we evaluated likely explanatory clinical and methodological study characteristics, to examine whether they could explain the heterogeneity observed.

When pooling was performed, we present summary estimates derived using both fixed effect and random effect models as a sensitivity analysis. Furthermore, for count outcomes, we calculated a summary of the relative effect (odds ratio) and absolute effect (risk difference). When the results from statistical testing were similar, we present the outcome that we judged to be most clinically relevant. We also present the number-needed-to-treat (NNT), when effects are statistically significant. In calculating the NNT, we used either the inverse of the risk difference (when risk difference is presented as the pooling measure, or the inverse of an estimated difference based on an average control event rate and a relative measure of effect (when odds ratio is used as the measure for pooling).

Results

Our searches of the literature identified a total of 1182 citations. Table 2 details the number of citations identified from each source.

Table 2. Sources of citations

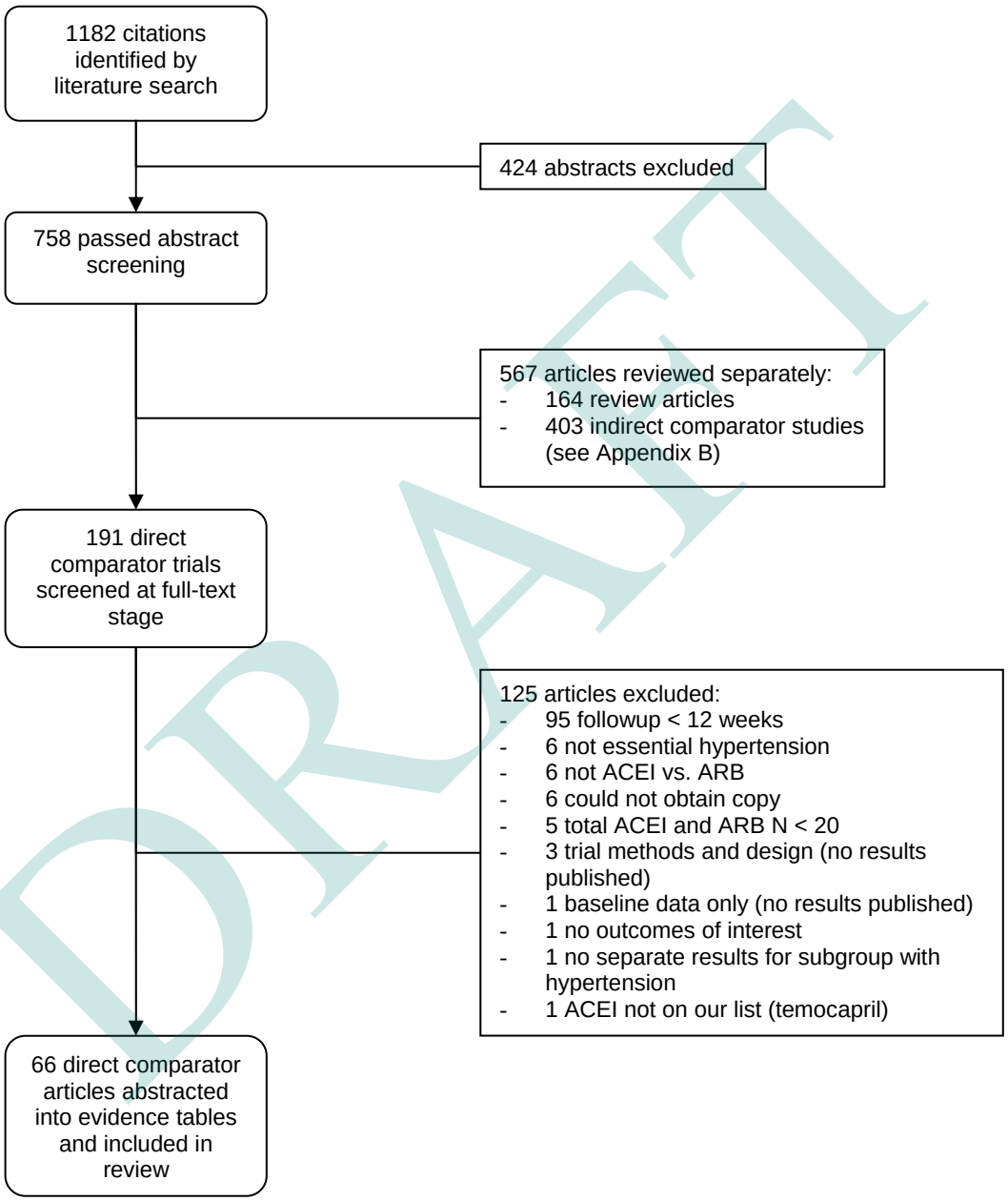
Source	Number of citations
MEDLINE®	1078
Cochrane Central Register of Controlled Trials	45
Register of systematic reviews underway in the Cochrane Hypertension Group	0
References of review articles and primary studies	23
Scientific information packets submitted by pharmaceutical companies	17
Other (recommendations from staff at AHRQ or SRC or from project investigators)	19
Total:	**1182**

Figure 1 describes the flow of literature through the screening process. Four hundred and twenty-four (424) citations were excluded at the abstract screening stage. Of the 758 citations that passed the abstract screening, 164 were review or methods articles, 136 were studies of ACEIs versus other (non-ARB) comparators, 267 were studies of ARBs versus other (non-ACEI) comparators, and 191 were direct comparator studies of ACEIs versus ARBs.

The remainder of this section describes results for the direct comparator studies. As stated above and described in Appendix B, we considered incorporating evidence from indirect studies for important outcomes that were under-reported in the direct comparator trials, but we were unable to identify a pool of comparable ACEI and ARB studies for this analysis.

At the full-text screening stage, 125 of the 191 direct comparator studies were excluded for the reasons summarized in Figure 1, leaving a total of 66 included articles. Appendix G provides a complete list of excluded head-to-head studies, with reasons for exclusion.

Figure 1. Literature flow diagram



The 66 included direct comparator articles reported on 58 distinct studies. Forty-six (46) of these were RCTs, one was a non-randomized controlled trial, seven were retrospective cohort studies, two were prospective cohort studies, and one study each was a cross-sectional cohort and a case-

control study. Table 3 describes the number of studies evaluating various possible treatment comparisons.

Table 3. Number of included studies (number of publications) evaluating various treatment comparisons*

ACEIs	ARBs								
	"ARBs"	**Candesartan cilexetil**	**Eprosartan**	**Irbesartan**	**Losartan**	**Olmesartan medoxomil**	**Telmisartan**	**Valsartan**	**Totals**
"ACEIs"	8 (10)	1 (1)	0	2 (2)	2 (2)	0	0	0	13 (15)
Benazepril	0	0	0	0	0	0	0	0	0
Captopril	0	0	0	0	2 (2)	0	0	0	2 (2)
Enalapril	0	4 (4)	2 (6)	4 (4)	9 (11)	0	2 (2)	1 (1)	22 (28)
Fosinopril	0	0	0	2 (2)	1 (1)	0	0	0	3 (3)
Lisinopril	0	4 (4)	0	0	0	0	1 (1)	2 (2)	7 (7)
Moexipril	0	0	0	0	0	0	0	0	0
Perindopril	0	1 (1)	0	0	1 (1)	0	2 (2)	0	4 (4)
Quinapril	0	0	0	0	2 (2)	0	0	0	2 (2)
Ramipril	0	0	0	0	0	0	3 (3)	0	3 (3)
Trandolapril	0	0	0	0	1 (1)	0	0	0	1 (1)
Totals:	8 (10)	10 (10)	2 (6)	8 (8)	18 (20)	0	8 (8)	3 (3)	-

*Also included was 1 study (1 publication) comparing a fixed combination of enalapril + hydrochlorothiazide (HCTZ) versus a fixed combination of losartan + HCTZ.

As Table 3 illustrates, enalapril was by far the most frequently studied ACEI (22 studies) and losartan the most frequently studied ARB (18 studies), followed by candesartan cilexetil (10 studies). The most commonly studied treatment comparison was enalapril versus losartan (9 studies), followed by the more generic "ACEIs" versus "ARBs" (8 studies). Other treatment comparisons were fairly sparsely represented.

In terms of quality, 37 studies were rated as fair, 16 as poor, and 5 as good. The distribution of studies by followup time is given in Table 4.

Table 4. Distribution of included studies by followup time

Treatment duration/followup time	Number of studies
12 weeks	19
14-16 weeks/3-4 months	8
24-26 weeks/6 months	13
10-11 months	2
48 weeks	3
1 year	6
15 months	1
720 days	1
3 years	3
39 months	1
4 years	1

There was no obvious correlation between study quality and length of followup. The five good-quality studies varied in length from 12 weeks (2 studies) to 16 weeks (1 study) to 1 year (2 studies).

Key Question 1. For adult patients with essential hypertension, how do ACEIs and ARBs differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes?

Key Points

- There was no clear difference in the blood pressure lowering efficacy between ACEIs and ARBs.
- Few deaths or major cardiovascular events occurred in the identified studies comparing ACEIs to ARBs; this precluded any assessment of a differential effect of ACEIs and ARBs on these events.
- No significant difference was observed between ACEIs and ARBs in terms of their impact on quality of life.

- A minimally increased rate of use of a second antihypertensive was noted for patients receiving an ACEI compared to an ARB.
- Available evidence suggests that ACEIs and ARBs have a similar lack of impact on lipid levels for individuals with essential hypertension.
- Available evidence suggests that ACEIs and ARBs have a similar lack of impact on glucose levels or HgbA1c for individuals with essential hypertension.
- Evidence does not demonstrate a difference between ACEIs and ARBs with regard to their effect on LV mass or function for individuals with essential hypertension.
- There are no consistently demonstrated differential effects related to renal function as measured by creatinine or GFR with use of ACEIs versus ARBs.
- There is a consistent finding of no differential effect related to reduction of urinary protein or albumin excretion among patients with essential hypertension with use of ACEIs versus ARBs.

Effect on Blood Pressure

Forty-nine (49) studies met our inclusion criteria and reported a blood pressure outcome. Of these, five (10 percent) were of good methodological quality, 31 (63 percent) were of fair quality, and 13 (27 percent) were of poor quality. There were 45 RCTs, two non-randomized controlled clinical trials, and one retrospective cohort and case-control study each. Sample sizes for individual studies ranged from 29 to 2416 patients, with a total of 16,347 patients. Study durations ranged from 12 weeks to 3.3 years, with a median of 16 weeks.

The mean age of study participants ranged from 38 years to 73 years, with a median of 54 years. The proportion of female patients included ranged from 19 to 100 percent, with a median of 47 percent. Only 23 (47 percent) studies reported the racial demographics of the study participants. Of these 23 studies, only eight (35 percent) enrolled a minimum of 10 percent of ethnic minority participants. Five of the studies (10 percent) were conducted in part or entirely within the United States, with the remainder carried out in other countries. The funding source was reported in only 27 studies (55 percent), with the majority of these (22 studies) funded by the manufacturer of one of the study medications.

The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the beginning of each study ranged from 141 to 181 mm Hg and 84 to 119 mm Hg respectively, with a median starting blood pressure was 158.3/99.8 mm Hg. There was significant heterogeneity in the study protocols and data reporting. Fewer than half of the studies (22/49; 45 percent) did not allow additional hypertension medications during the study; 18/49 (37 percent) allowed additional medications according to a specified protocol; 4/49 (8 percent) allowed additional medications at the discretion of the treating physician; and 5/49 (10 percent) studies did not report concomitant hypertension therapy. The reported blood pressure endpoints varied as well, with 13/49 (26 percent) reporting mean change in blood pressure and final posttreatment blood pressure; 19/49 (39 percent) reporting only final posttreatment blood pressure; 14/49 (29 percent) reporting only mean change in blood pressure in each study arm; and 3/49 (6 percent) not providing quantitative data for the blood pressure outcome or reporting only the proportion of patients achieving a target blood pressure.

For the overall comparison of blood pressure lowering between ACEIs and ARBs, 35 studies reported no difference (71 percent), two studies favored ACEIs (4 percent), nine studies favored ARBs (18 percent), and three studies (6 percent) did not report the comparison between the two agents. We did not detect any specific ACEI or ARB that performed better or worse than the other medications in its class.

Blood pressure outcomes were confounded by protocols calling for dose escalation or adding additional blood pressure lowering drugs; such protocols differed substantially between studies, making the blood pressure outcomes difficult to interpret. Overall, there was no clear difference in the blood pressure lowering efficacy between the two classes of agents, no matter what criteria were used for study inclusion. Because of the heterogeneity in study protocols, quantitative meta-analysis was not performed. However, despite some differences in methods for measuring successful control of blood pressure on a single agent, this outcome seemed to represent a reasonable comparison that was not confounded by substantial differences between studies. Therefore, quantitative meta-analysis was performed for this outcome.

Caveats and concerns include the fact that there was significant heterogeneity in the medication protocols and the use of concomitant hypertension therapy. Many of the studies reported limited data on patient characteristics, and black patients appeared to be significantly underrepresented overall. Very few of the studies were considered to be of good methodological quality. In addition, the majority of the studies reporting a funding source were sponsored by the manufacturer of the ARB.

Effect on Mortality and Major Cardiovascular Events

The literature review identified 12 publications[10-21] describing eight studies that reported patient mortality, MI, or clinical stroke as outcomes. All eight studies were RCTs. They included over 3,800 patients and ranged in duration from 12 weeks to 3 years, and most reported blood pressure measurements as primary endpoints. The treatment comparisons studied were: candasartan versus enalapril, erposartan versus enalapril, losartan versus enalapril, losartan versus fospinopril, telmisartan versus ramipril, and valsartan versus lisinopril.

In general the studies were of fair quality. Notably, the majority of studies in this review – including those reporting morality and major cardiovascular events – excluded patients with significant cardiovascular disease and often other co-morbid conditions.

The included studies shed little light on the issue of relative rates of mortality, MI, or stroke with ACEIs versus ARBs. In eight studies involving more than 3,800 patients, four patients died. The study by Ruilope et al.,[16] evaluating erposartan versus enalapril over 12 weeks, reported one death in each group, a 95-year-old patient with cancer and an 80-year-old patient with heart failure. Shibaskaki et al.[18] evaluated losartan versus enalapril over 6 months and reported one death due to pulmonary hemorrhage, and one patient with MI; the treatment group to which the patient belonged was not specified for either event. The paper by Elliott et al.[11] is the primary report of a trial of erposartan versus enalapril over 26 weeks. A substudy from this trial published by Gavras et al.[12] reported that one patient assigned to the eprosartan group had a anteroseptal MI and died. Finally, Williams et al.[20] evaluated telmisartan versus ramipril over 14

weeks and reported that one patient in the ramipril group had a stroke. In none of these trials did investigators attribute any of the events observed directly to therapy.

Give the importance of this long-term outcome and the absence of significant data on major cardiovascular events, we tuned to the indirect evidence (i.e., comparing an ACEI and an ARB to a common comparator, but not to each other.) However, the evidence was not deemed suitable for any indirect comparison (see Appendix B). In particular, a key risk factor for events – namely mean subject age – was widely discrepant in the small pool of potential indirect studies.

Effect on Quality of Life

Four studies described in eight separate papers met our inclusion criteria and reported quality of life.[10-14,22-24] All four were RCTs and were rated as fair in methodological quality. However, with regard to assessing quality of life, two of the four could be considered poor, as they did not present quantitative data.[22,24]

Sample sizes for the individual studies ranged from 42 to 528 patients, with a total of 1134 patients. Study durations ranged from 12 weeks to 3 years, with a mean of 55 weeks (median 26 weeks). Only one of the four studies reported the racial demographics of the study participants;[11] in that study, 14 percent of participants were members of ethnic minorities. Studies utilized a variety of quality-of-life scales: two administered the Psychological General Well Being with its six subscales;[11,24] two administered the Subjective Symptoms Assessment profile; [11,23] one study employed the MacMaster Overall Treatment Evaluation Questionnaire;[24] and one used the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36).[22] Only two studies presented any quantitative data to support their conclusions of no difference in the impact of ACEIs or ARBs on quality of life.[11,23]

None of the studies found any difference between ACEIs and ARBs in their impact on the quality of life of study participants; indeed, no study demonstrated an impact on quality of life for subjects treated with ACEIs *or* ARBs.

Effect on Rate of Use of a Single Antihypertensive Agent

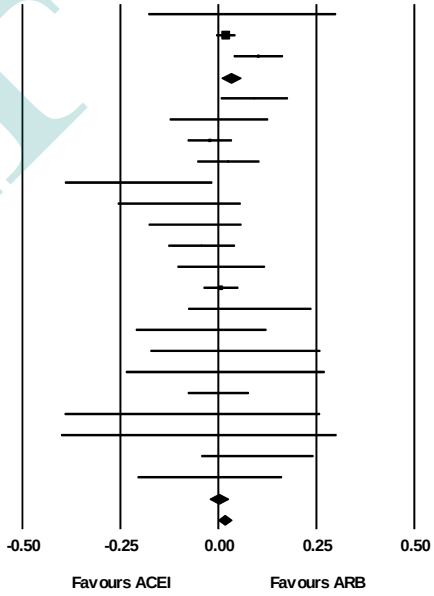
We identified 22 studies that reported the outcome of successful monotherapy with an ACEI or ARB.[10,16,17,19,21,22,25-40] The definition of "successful" monotherapy differed between studies and included SBP or DBP below a specified cutoff, or monotherapy defined by a lack of additional antihypertensive medication at the end of the study. Three of these studies were determined to be good quality, 15 were fair in quality, and four were poor. There were 19 RCTs, two retrospective cohorts, and one case-control study. Sample sizes ranged from 30 to 13,303 patients, with a total of 21,562 patients. Study durations ranged from 12 weeks to 3.3 years, with a median of 26 weeks. The rates of successful monotherapy ranged between 6 percent and 93.3 percent (median 61%). The average proportion for successful monotherapy across all studies was 55.9 percent for both ACEIs and ARBs.

We performed a meta-analysis of data from the 22 studies (Figure 2). Individual study estimates for the differences between ACEIs and ARBs in the proportion of patients achieving successful

blood pressure control on a single agent showed no statistical heterogeneity (I^2 = 18 percent; Q = 25.8; d.f. = 21; p = 0.22). A summary estimate of the difference in the proportion of patients with successful blood pressure control on a single agent was one percent (95 percent CI 0 to 3 percent; p = 0.08; fixed-effect model; results based on odds ratios and median incidence are similar (results not shown)). Because the definition of successful control of blood pressure with a single agent requires a patient remain on the originally prescribed drug and receive no additional antihypertensive agent, "successful monotherapy" reflects both the efficacy of the medication and tolerability and adherence to the prescribed therapy. The advantage of ARBs for this outcome appeared to be driven primarily by difference in tolerability and adherence, since the benefit of ARBs was heavily influenced by retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients, or RCTs with very loosely defined protocols for medication titration and switching.

Figure 2. Successful monotherapy with ACEIs vs. ARBs

Group by Study design	Outcome	Study name	Time point	Risk difference	Lower limit	Upper limit	p-Value
OBS	Monotherapy	Verdecchia	172 weeks	0.06	-0.18	0.30	0.62
OBS	Monotherapy	Mazzaglia	52 weeks	0.02	-0.01	0.04	0.15
OBS	Monotherapy	Hasford	52 weeks	0.10	0.04	0.17	0.00
OBS				0.03	0.01	0.05	0.01
RCT	Monotherapy	Saito	26 weeks	0.09	0.01	0.18	0.04
RCT	Monotherapy	Cuspidi	48 weeks	0.00	-0.13	0.13	0.99
RCT	Monotherapy	Ruilope	12 weeks	-0.02	-0.08	0.04	0.46
RCT	Monotherapy	Larochelle	12 weeks	0.03	-0.06	0.11	0.54
RCT	Monotherapy	Lacourciere	52 weeks	-0.20	-0.39	-0.01	0.03
RCT	Monotherapy	Ruff	12 weeks	-0.10	-0.26	0.06	0.21
RCT	Monotherapy	Townsend	12 weeks	-0.06	-0.18	0.06	0.33
RCT	Monotherapy	Neutel	48 weeks	-0.04	-0.13	0.04	0.33
RCT	Monotherapy	Karlberg	26 weeks	0.01	-0.11	0.12	0.90
RCT	Monotherapy	Malacco	16 weeks	0.01	-0.04	0.05	0.78
RCT	Monotherapy	Fogari	16 weeks	0.08	-0.08	0.24	0.32
RCT	Monotherapy	Rosei	24 weeks	-0.04	-0.21	0.12	0.61
RCT	Monotherapy	Ghiadoni	26 weeks	0.04	-0.17	0.26	0.70
RCT	Monotherapy	Uchiyama-Tanaka	52 weeks	0.02	-0.24	0.27	0.89
RCT	Monotherapy	Argenziano	26 weeks	0.00	-0.08	0.08	1.00
RCT	Monotherapy	Robles	12 weeks	-0.07	-0.39	0.26	0.69
RCT	Monotherapy	Kavgaci	26 weeks	-0.05	-0.40	0.30	0.78
RCT	Monotherapy	Mogensen	24 weeks	0.10	-0.04	0.24	0.18
RCT	Monotherapy	Eguchi	12 weeks	-0.02	-0.21	0.16	0.82
RCT				-0.00	-0.02	0.02	0.99
Overall				0.01	-0.00	0.03	0.08



Effect on Lipid Levels

Twelve studies described in 17 papers met our inclusion criteria and evaluated lipid changes. Eleven of the 12 studies were RCTs;[11,15,17,19,28,35,39,41-44] one was an observational case-control study.[40] The ACEI-versus-ARB treatment comparisons were unique in nine studies and similar (losartan versus enalapril) in three.[17,40,44] Study periods ranged from 3 to 12 months, all of which were sufficiently long to detect measurable changes in the lipid profile.

Most of the 12 studies were fair in quality and none addressed the use of lipid-lowering agents during the study period. The two studies rated as good in quality[15,41] were moderately sized (70

and 96), 1-year investigations of Europeans with diabetes; however, they differed in mean age, proportion of females, recruitment settings, and time of onset of diabetes.

The majority of the available head-to-head evidence suggests that ACEIs and ARBs have a similar lack of impact on lipid parameters. Six studies directly compared outcomes between ACEI and ARB groups.[35,40-44] One study reported a decrease in LDL that was statistically greater in the ACEI group (perindopril -14 percent versus candesartan -4 percent),[41] and one reported a statistically significant greater percentage of individuals with an increase in LDL in the enalapril group than in the candesartan group (19.3 percent versus 11.5 percent).[35] Thus, for the two studies for which a difference was found, the difference was discrepant (i.e., an increase in LDL in one and a decline in LDL in the other). The remaining four studies that analyzed differences in outcomes between the two groups did not find a difference.

Nine studies found no change in total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), or triglyceride (TG) levels during the study period. The remaining three studies detected a small but statistically significant change in TC (two studies[17,19]), LDL (one study[41]), and TG (one study[19]) (Table 5). The magnitude of these changes was equivalent for the compared medications except for one of the TC studies (ARB favored)[19] and the LDL study (ACEI favored).[41] Of these, only one was rated as good in quality.[41]

Table 5. Studies evaluating lipid profile changes

Study	N	Population	Quality	Comparators	ΔTC	ΔLDL	ΔHDL	ΔTG
Lacourciere et al.[17]	103	- Mean age 58 - 96% white - Canada - Diabetes	Fair	Losartan vs. enalapril	-2.1% +4.2%*	NR	NR	NR
Derosa et al.[41]	96	- Mean age 54 - 100% white - Europe - Diabetes	Good	Candesartan vs. perindopril	NR	-4% -14%*	+2% -2%	+2% -22%
Kaygaci et al.[19]	33	- Mean age 53 - 100% white - Turkey - Diabetes	Poor	Losartan vs. fosinopril	+0.01% -0.1%*	NR	NR	-0.23%* -0.21%*

*Statistically significant change (baseline to followup)

Abbreviations: HDL = low-density lipoprotein; LDL = low-density lipoprotein; N = number of subjects; NR=not reported; TC = total cholesterol; TG = triglyceride

The study by Schram et al.,[15] a broad-based community study comparing candesartan to lisinopril, found no change in lipid levels, while the study by Derosa et al.[41] comparing candesartan to perindopril in newly diagnosed diabetics attending a university-based internal medicine outpatient clinic found an improvement in LDL (favoring perindopril, -14 percent versus -4 percent), but no change in other lipid parameters. The broader population of the first

study makes it more generalizeable; however, it allowed the sequential addition of specified antihypertensives to achieve a goal blood pressure. This heterogeneity in medication use makes attributing the outcomes to any single agent difficult. Both studies are limited by a failure to include races other than Caucasians. There were two large studies, one of 407[44] and one of 528 subjects.[11] Both were rated as fair in quality and neither detected a change in lipid parameters.

Effect on Markers of Carbohydrate Metabolism/Diabetes Control

Thirteen studies described in 18 papers met our inclusion criteria and measured glucose or HgbA1c. All but two[40,45] were RCTs. Overall, only two studies were rated as good in quality;[15,41] the remainder were rated as either fair (seven studies[11,17,32,39,42-44]) or poor (four studies[19,28,40,45]). The ACEI-versus-ARB comparisons tested were unique in seven studies; of the remaining six studies, enalapril and losartan were compared in four,[17,40,44,45] and candesartan and lisinopril in two.[15,32]

It is relevant that none of the 13 studies measuring glucose or HgbA1c changes addressed hypoglycemic therapy during the study period, and only six were specifically performed in diabetic populations.[15,17,19,32,41,42] Of the other seven studies, three permitted controlled diabetic patients but did not describe their proportion in the cohort;[11,40,44] one permitted diabetic subjects, but they were in the minority (26 percent of subjects);[39] and three specifically excluded individuals with diabetes.[28,43,45]

The majority of the available head-to-head evidence suggests that ACEIs and ARBs have a similar lack of impact on glucose levels or HgbA1c. Six studies directly compared outcomes between the ACEI and ARB groups.[40-45] One study reported a small decrease in glucose that was statistically greater in the ACEI group (perindopril -15 ± 4 mg/dL, candesartan -8 ± 2 mg/dL),[41] and one reported a significant increase in HgbA1c (+0.25 percent enalapril versus +0.6 percent losartan) but did not directly compare the two groups.[17] Of these two studies only the former[41] was rated as good in quality. The other five studies that analyzed differences in outcomes between the two groups did not find a difference. Eleven studies compared baseline to followup glucose levels or HgbA1c and found no change for either the ACEI or ARB groups.

Effect on Measures of LV Mass or Function

Eight studies presented results on left ventricular (LV) mass or function assessed either by LV mass index (LVMI; 3 studies),[23,40,45] LV ejection fraction (LVEF; 2 studies),[46,47] or both (3 studies).[18,25,48] Table 6 summarizes relevant characteristics of all eight studies. Half of these studies had fewer than 50 patients,[18,23,45,46] while the other half had 100 or more patients.[25,40,47,48] All but two studies[40,45] were RCTs. Only two studies had relatively long-term followup (≥ 3 years);[23,40] however, the majority of studies had between 6 and 12 months of followup,[18,25,45,47,48] while one study had only 3 months of followup.[46] Because duration of therapy may significantly impact the ability to observe changes in LV mass or LV function, negative results must be interpreted with caution in studies with short-term followup.

Table 6. Characteristics of studies reporting LV mass/function outcomes

Study	Agents studied	Population	Design and size*	Duration	Quality	Outcome	Result
Cuspidi et al.[25]	Candesartan vs. enalapril	LVH (29-32%)	RCT N = 196 (145)	48 wk	Fair	LVMI & LVEF	↓LVMI both, no difference between agents, no change in LVEF
Schieffer et al.[46]	Irbesartan vs. enalapril	CAD (? %LVH)	RCT N = 60 (48)	3 mo	Poor	LVEF	No difference
Avanza et al.[45]	Losartan vs. enalapril	LVH (100%)	Non-rand controlled clinical trial N = 30	10 mo	Poor	LVMI	↓LVMI both, no difference between agents, combo ACEI/ARB best
De Rosa et al.[23]	Losartan vs. enalapril	LVH (44-53%)	RCT N = 50 (42)	3 yr	Fair	LVMI	Non-statistical ↓LVMI both, no difference between agents
Shibasaki et al.[18]	Losartan vs. enalapril	ESRD with LVH (100%)	RCT N = 20	6 mo	Fair	LVMI & LVEF	↓LVMI both, ARB better than ACEI, no change in LVEF
Verdecchia et al.[40]	Losartan vs. enalapril	LVH (23-24%)	Case-control N = 88	3.3 yr	Poor	LVMI	↓LVMI both, no difference between agents
Rajzer et al.[48]	Losartan vs. quinapril	HTN (? %LVH)	RCT N = 118	6 mo	Poor	LVMI & LVEF	No change in LVMI or LVEF in either group
Celik et al.[47]	Telmisartan vs. ramipril	HTN (? %LVH)	RCT N = 100	6 mo	Poor	LVEF	No change in LVEF in either group

* Size of study includes total enrolled, with followup population (if different) in parentheses.

Abbreviations: CAD = coronary artery disease; ESRD = end-stage renal disease; HTN = hypertension; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; mo = months; RCT = randomized controlled trial; wk = weeks; yr = years

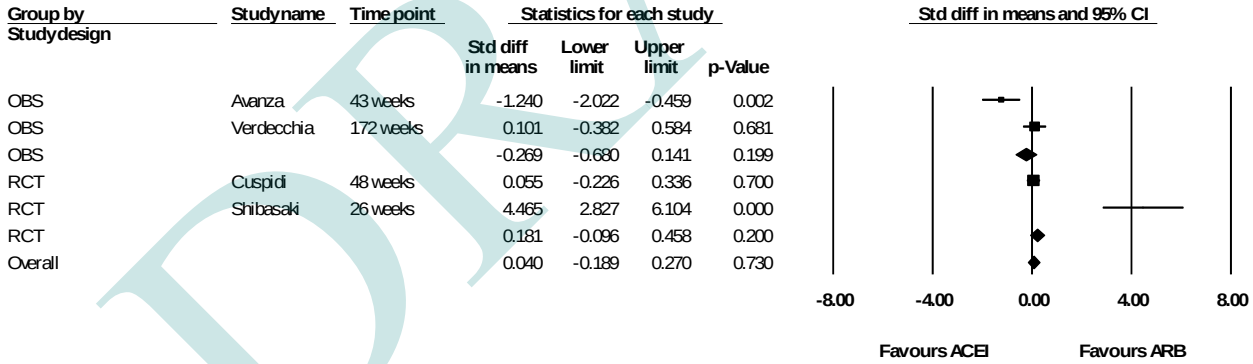
Evidence provided by the eight studies identified did not demonstrate a difference between ACEIs and ARBs with regard to LV mass or function for individuals with essential hypertension. Six studies reported detailed data by treatment groups, [18,23,25,40,45,47] while one reported summary data,[48] and one described changes without presenting any data.[46] In general, the quality ratings of these studies describing changes in LV mass or function was poor. None was rated as being a good-quality study, while the majority (n = 5) were assessed to be of poor quality.[40,45-48] Various ARBs were studied, including five studies with losartan[18,23,40,45,48] and six studies with enalapril.[18,23,25,40,45,46] Among the six studies that presented detailed data on outcomes, three assessed LVMI,[23,40,45] one assessed LVEF,[47] and two assessed both LVMI and LVEF.[18,25]

The best and largest comparative study assessed LVMI and LVEF at baseline and after 48 weeks of followup.[25] The authors reported similar decreases in mean LVMI in both groups in both

intention-to-treat and per-protocol analyses (36.3 percent on candesartan with normalized LVMI versus 28.6 percent on enalapril). No significant changes were observed for LVEF. The trial with the longest followup (3 years) also reported similar reductions in mean LVMI in both groups; however, these changes did not reach statistical significance.[23] Two non-randomized studies reported similar decreases in LVMI,[40,45] with one[45] demonstrating additional benefit in LVMI reduction with combination ACEI and ARB therapy. Only one study demonstrated a difference between groups for reduction in LVMI,[18] with lower reduction among those treated with losartan versus enalapril (24.7 ± 3.2 percent versus 11.2 ± 4.1 percent; p = 0.026). However, definitive conclusions from this study are limited because it was conducted in patients with end-stage renal disease, included only 10 patients in each group, and had only moderate duration of followup. Finally, among the studies that reported results for LVEF, none demonstrated any differential effects between the ACEI and ARB groups.

These data are summarized in a forest plot (Figure 3). Despite differences in sample size, study design, length of followup, study quality, therapeutic agents, and outcome measure, most of the studies demonstrated either similar improvements in LV mass or function between the ACEI and ARB groups[18,25,40,45] or no change.[23,48] Reductions in LVMI appear to have occurred particularly among patients with established LV hypertrophy.[18,23,25,45] No changes in LVEF were observed in any of the studies. As a result, this body of poor- to fair-quality evidence consistently demonstrates that there are no differential effects in the ability of ACEIs and ARBs to reduce LVMI, and that neither has a significant effect on improving LVEF in patients with essential hypertension.

Figure 3. Studies evaluating LVMI for ACEIs vs. ARBs



Effect on Serum Creatinine/GFR and Proteinuria

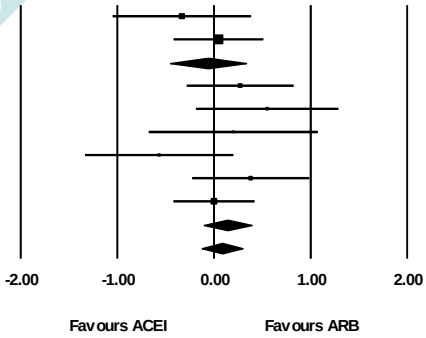
Review of the literature on the relative effects of ACEIs and ARBs on changes in renal intermediate outcomes identified 19 studies described in 25 papers. Ten studies assessed either serum creatinine or GFR;[11,18,23,39,40,42,45,49-51] four assessed proteinuria;[15,32,41,52] and five assessed both.[17,19,35,44,53] Most of these studies included fewer than 100 patients; however, five had about 200 patients or greater.[11,32,44,49,50] All but three[40,45,52] were RCTs. Approximately half of the studies had at least 1 year of followup; however, four studies followed patients for less than 4 months.[42,44,49,51]

The 15 studies that described changes in creatinine or GFR did not consistently demonstrate differential effects related to renal function with use of ACEIs versus ARBs. Nine of these studies reported detailed data by treatment groups, while two reported summary data[17,44] and four described the changes without presenting any data.[11,35,50,53] Among the nine studies that reported data on renal function, none were rated as being good-quality studies; four were of poor quality;[19,40,45,51] two were non-randomized studies;[40,45] and only one had over 100 patients.[49] All but one[49] compared losartan with a specific ACEI, the majority of which used enalapril as the comparator.[18,23,40,45,51]

The best comparative study assessed GFR by renal scintigraphy at baseline and after 3 years of followup.[23] The authors reported increases in mean GFR in both groups, but a statistically significant increase only among those treated with losartan compared with enalapril. The largest study in this group (n = 190) reported a greater short-term increase (12-week study) in mean serum creatinine in the enalapril group (change 0.03 mg/dL [95% CI 0 to 0.06]) compared with the irbesartan group (change 0.01 mg/dL [95% CI -0.02 to 0.04]).[49] Nonetheless, serum creatinine remained unchanged before and after treatment in all the other studies that reported it as an outcome (Figure 4).

Figure 4. Studies evaluating renal function for ACEIs vs. ARBs

Group by Study design	Study name	Outcome	Time point	Std diff in means	Lower limit	Upper limit	p-Value
OBS	Ananza	Creatinine (mg/dL)	43 weeks	-0.333	-1.054	0.387	0.365
OBS	Verdecchia	Creatinine (mg/ml)	83 weeks	0.045	-0.423	0.514	0.849
OBS				-0.067	-0.460	0.326	0.738
RCT	Derosa	GFR (ml/min)	156 weeks	0.271	-0.287	0.828	0.341
RCT	Shand	CCl (ml/min)	17 weeks	0.550	-0.192	1.292	0.146
RCT	Shibasaki	Creatinine (mg/ml)	26 weeks	0.200	-0.679	1.079	0.656
RCT	Kavgaci	CCl (ml/min)	26 weeks	-0.567	-1.340	0.205	0.150
RCT	Uchiyama-Tanaka	Creatinine (mg/dl)	52 weeks	0.380	-0.231	0.991	0.223
RCT	Fogari	Creatinine (mg/dl)	12 weeks	0.000	-0.425	0.425	1.000
RCT				0.135	-0.113	0.384	0.285
Overall				0.078	-0.132	0.288	0.468

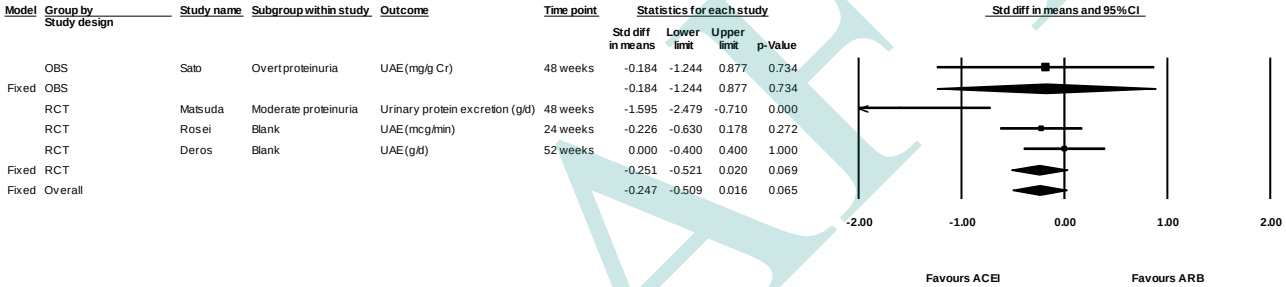


Key to Figure 4: CCl = creatinine clearance; GFR = glomerular filtration rate

Of two poor-quality studies that reported on changes in creatinine clearance, one reported no change.[51] Although the other study reported significant and similar decreases in creatinine clearance in both groups,[19] these changes did not correspond to the changes in serum creatinine reported, which calls into question the reliability of the data. Of the two studies that reported summary data, one found a nine percent mean decline in GFR assessed by radio-labeled excretion in each group ($p < 0.001$ at 52 weeks),[17] while the other found no change in mean percent change in serum creatinine.[44] Of the four studies that did not present data, two reported that there were no overall differences between groups;[35,53] another that the degree and direction of non-significant change in renal function were comparable in both treatment groups;[11] and the last described that 2 out of 192 patients treated with losartan developed an increase in serum creatinine during the 12-week study.[50]

The nine studies that described changes in urine albumin or protein excretion consistently demonstrate no differential effects related to reduction of urinary protein or albumin excretion among patients with essential hypertension with use of either ACEIs or ARBs. Overall fair in quality, eight of nine studies reported detailed data by treatment groups, while one reported summary data in graphical format.[15] Among the eight studies that reported data, one was rated as being a good-quality study,[41] three were of poor quality;[19,52,53] one was a non-randomized cohort study;[52] and only two studies had more than 100 patients.[32,44] Various ARBs were used, including four studies with candesartan,[32,35,41,52] three with losartan,[17,19,44] and one with both.[53] All studies assessed urinary albumin excretion except for one study that assessed urinary protein excretion.[53] Studies also varied in length of followup ranging from 12 weeks to 1 year. However, despite these differences in study quality, sample size, therapeutic agents, outcome measure and length of followup, all of the studies demonstrated declines in urinary protein/albumin excretion that were similar between the ACEI and ARB groups (demonstrated graphically in Figure 5).

Figure 5. Studies evaluating urinary protein excretion for ACEIs vs. ARBs



Key to Figure 5: UAE = urinary albumin excretion

The lack of an apparent differential impact of ACEIs versus ARBs on intermediate renal parameters must be considered in light of concerns about the available literature. Some concerns may reinforce the conclusion. For example, the study by Matsuda et al.[53] provided sufficient data only on the subgroup of patients with moderate proteinuria and thus would likely favor ACEIs, yet there were no significant differential effects between the ACEI and ARB groups within the entire study sample after 48 weeks ($p > 0.5$). Four additional studies that also failed to demonstrate a differential effect could not be included in the meta-analysis due to the format of the data presented.[17,19,32,44] On the other hand, because duration of therapy may significantly impact the ability to observe meaningful changes in renal function or proteinuria, negative results must be interpreted with caution in studies with short-term followup.

Key Question 2. For adult patients with essential hypertension, how do ACEIs and ARBs differ in safety, adverse events, tolerability, persistence, and adherence?

Key Points

- Cough was modestly more frequently observed as an adverse event in groups treated with ACEIs than in groups treated with ARBs.
- Withdrawals due to adverse events were modestly more frequent for groups receiving an ACEI rather than an ARB; this is consistent with differential rates of cough.
- No significant between-class differences were observed in the rates of any other commonly reported adverse events.
- Adherence – in terms of pill counts in RCTs – is similarly high with both ACEIs and ARBs. However, persistence is generally lower with ACEIs, which appears to be explained largely by withdrawals due to cough (as above).

Safety and Adverse Events

Rates of Serious and Overall Adverse Events

Seven studies met our inclusion criteria and reported overall rates of serious adverse events.[20-22,35,49,50,54] One of these studies was rated as good in methodological quality, and the remaining six were fair. However, the nature of serious adverse event reporting was inconsistent, and rates of serious adverse events were low (on the order of 0 to 6 percent, depending on definition); thus, data on these events were not deemed useful for assessing a differential effect of ACEIs versus ARBs.

Similarly, of the 28 studies that met inclusion criteria and reported overall adverse event rates,[11,16,20-22,24-27,30,33,35,36,38,41,44,49-51,54-62] most were assessed as being fair (21 studies) or poor (four studies) in quality, and there was significant variation in the manner in which adverse events were reported. Depending on the definition used, adverse event rates ranged from 0 to 76 percent (median 32 percent) for ACEIs, and 0 to 79 percent (median 27 percent) for ARBs. Thus, data on overall rates of adverse events were not considered further.

Specific Adverse Events

Thirty studies reported rates of one or more specific adverse events,[11,16,17,20-25,27,30,33,36,38,41,44,49,50,52,54,56-65] including cough (29 studies), headache (21 studies), dizziness (18 studies), fatigue (10 studies), upper respiratory infection (6 studies), and nausea (6 studies). Viral infection, ankle edema, and back pain were reported as adverse events by three studies each. Palpitations, myalgia, diarrhea, malaise, and hypotension were reported by two studies each. Accident/injury, pharyngitis, rhinitis, dyspnea, abdominal pain, abnormal taste, urinary tract infection, constipation, dry mouth, feeling sick, pyrosis, insomnia, fever, asthenia, impotence, dyspepsia, musculoskeletal pain, flatulence, epigastric discomfort, increased sweating, erythematous rash, rhinitis, sinusitis, vertigo, flushing, cold hands/feet, adverse events

related to the nervous system, adverse events related to the cardiovascular system, and adverse events related to the gastrointestinal system were reported as a specific adverse events by one study each.

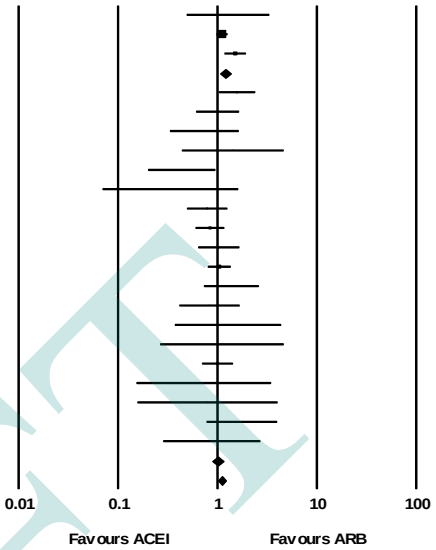
Given the large number of commonly reported specific adverse events, we focused on three specific events with the largest difference in absolute rates across studies: cough, dizziness, and headache. The results revealed that rates for dizziness (risk difference 0.1 percent in favor of ACEIs, p = 0.805, fixed-effect model), and headache (risk difference 0.7 percent in favor of ARBs, p = 0.069, fixed-effect model) were not significantly different in the study participants treated either by ARBs or ACEIs. These results suggest that there is no differential impact of ACEIs and ARBs with regard to dizziness or headache.

The one adverse event for which significant differential effects were apparent is cough. Twenty-nine studies compared cough in subjects treated with ACEIs and ARBs. In terms of quality, four were rated as good, 21 as fair, and four as poor. Of the 29 studies, 27 were RCTs, one was a cross-sectional cohort study, and one a retrospective cohort study. Sample sizes for the studies ranged from 49 to 51,410 patients, with a total of 61,978 patients. Study durations ranged from 12 weeks to 3 years, with a median of 16 weeks. The mean patient age of study participants was 57 years (SD 6.25). The proportion of female patients included ranged from 19 to 100 percent. Eighteen studies (62 percent) reported the racial demographics of the study participants. Of these 18 studies, eight (44 percent) enrolled a minimum of 10 percent of ethnic minority participants.

Rates of cough in these studies ranged from 0 to 13 percent for ARB-treated groups (mean 3 percent, median 1 percent) and from 0 to 22 percent in ACEI-treated groups (mean 10 percent, median 9 percent). All 29 studies demonstrated higher rates of cough in ACEI- treated participants. For the meta-analysis of studies reporting cough as an adverse event, we included all studies that reported on cough rates (Figure 6). The Q test and the I^2 between studies demonstrated significant heterogeneity among the studies (Q = 207.291; I^2 = 86.493). Performing a meta-analysis using a random effects model leads to an estimated odds ratio of 0.341 in favor of ARBs (95 percent CI 0.297 to 0.392; p = 0.000). Notably, the observed rates of cough appear much higher in RCTs than cohort studies; this is due to the higher detection when the patient is queried systematically for this symptom. Thus, based on the overall odds ratio of 0.341, when we use the rate of cough with ACEIs equal to the RCTs (8.9%) the absolute rate difference is estimated 5.7% (NNT = 18); however, when we use the rate of cough with ACEIs equal to the cohort studies (2%) the absolute rate difference is estimated to be 1.3% (NNT = 76). The latter estimate is likely to be more clinically relevant.

Figure 6. Studies reporting on cough with ACEIs vs. ARBs

Group by Study design	Outcome	Study name	Time point	Odds ratio	Lower limit	Upper limit	p-Value
OBS	Monotherapy	Verdecchia	172 weeks	1.28	0.48	3.36	0.62
OBS	Monotherapy	Mazzaglia	52 weeks	1.11	0.96	1.27	0.15
OBS	Monotherapy	Hasford	52 weeks	1.51	1.16	1.96	0.00
OBS				1.19	1.05	1.34	0.01
RCT	Monotherapy	Saito	26 weeks	1.57	1.02	2.42	0.04
RCT	Monotherapy	Cuspidi	48 weeks	1.00	0.60	1.67	0.99
RCT	Monotherapy	Ruilope	12 weeks	0.74	0.33	1.66	0.46
RCT	Monotherapy	Larochelle	12 weeks	1.43	0.43	4.68	0.56
RCT	Monotherapy	Lacourciere	52 weeks	0.44	0.20	0.96	0.04
RCT	Monotherapy	Ruff	12 weeks	0.34	0.07	1.63	0.18
RCT	Monotherapy	Townsend	12 weeks	0.79	0.49	1.27	0.33
RCT	Monotherapy	Neutel	48 weeks	0.84	0.59	1.19	0.33
RCT	Monotherapy	Karlberg	26 weeks	1.03	0.63	1.68	0.90
RCT	Monotherapy	Malacco	16 weeks	1.04	0.79	1.37	0.78
RCT	Monotherapy	Fogari	16 weeks	1.38	0.72	2.64	0.32
RCT	Monotherapy	Rosei	24 weeks	0.83	0.41	1.69	0.61
RCT	Monotherapy	Ghiadoni	26 weeks	1.28	0.37	4.42	0.70
RCT	Monotherapy	Uchiyama-Tanaka	52 weeks	1.11	0.26	4.67	0.89
RCT	Monotherapy	Argenziano	26 weeks	1.00	0.69	1.45	1.00
RCT	Monotherapy	Robles	12 weeks	0.73	0.15	3.49	0.69
RCT	Monotherapy	Kavgaci	26 weeks	0.80	0.16	4.08	0.78
RCT	Monotherapy	Mogensen	24 weeks	1.76	0.77	4.04	0.18
RCT	Monotherapy	Eguchi	12 weeks	0.88	0.28	2.73	0.82
RCT				1.00	0.87	1.13	0.95
Overall				1.09	1.00	1.20	0.05



Withdrawals Due to Adverse Events

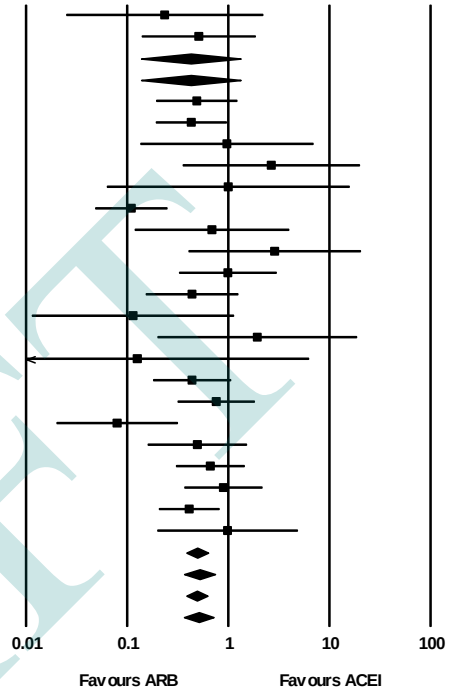
Twenty-three (23) studies met our inclusion criteria and reported withdrawals due to adverse events.[11,15,17,21-23,25,32,33,38,40,44,45,49-51,56-60,62,65] Of these, one (four percent) was of good methodological quality, 17 (74 percent) were fair in quality, and five (22 percent) were poor. Twenty-one studies were RCTs, one was a non-randomized controlled clinical trial, and one was a case-control study. Sample sizes for the individual studies ranged from 46 to 1213 patients, with a total of 7234 patients. Study durations ranged from 12 weeks to 3.3 years, with a mean of 24 weeks (median 25 weeks). The mean age of study participants was 55 years (SD 5). The proportion of female patients included ranged from 19 to 59 percent, with a mean of 46 percent. Fourteen studies (61 percent) reported the racial demographics of the study participants. Of these, six (26 percent) enrolled a minimum of 10 percent of ethnic minority participants, while five enrolled only white patients.

Rates of withdrawals due to adverse events ranged from 1 to 41 percent, with a mean of five percent (median seven percent) for patients on ARBs, and a mean of three percent for patients on ACEIs (median six percent). Trials almost uniformly favored ARBs (i.e., there were more withdrawals in ACEI-treated groups). However, there was significant variation in the study protocols and data reporting.

We conducted a meta-analysis of all 23 trials that reported withdrawals due to adverse events (Figure 7). Fourteen studies demonstrated higher rates in ACEI-treated participants; three studies demonstrated higher rates in ARB-treated participants; and six showed no difference in withdrawal rates. For the pooled odds ratio, the Q test and the I^2 between studies demonstrated modest heterogeneity between studies ($Q = 35.1$; $I^2 = 37\%$). The meta-analysis revealed that the odds ratio for withdrawal rate favored ARBs (0.50; 95% CI 0.36 to 0.70; random-effects model). For the median withdrawal rate (3.1% for ACEIs) the absolute difference in withdrawal rate is estimated to be 1.6% (NNT = 64).

Figure 7. Studies reporting withdrawals due to adverse events for ACEIs vs. ARBs

Model	Outcome	Group by Study design	Study name	Peto odds ratio	Lower limit	Upper limit	p-Value
	Withdrawals	OBS	Avanza	0.23	0.02	2.23	0.21
	Withdrawals	OBS	Verdecchia	0.51	0.14	1.90	0.32
Fixed		OBS		0.42	0.14	1.30	0.13
Random		OBS		0.42	0.14	1.30	0.13
	Withdrawals	RCT	Cuspidi	0.49	0.19	1.25	0.13
	Withdrawals	RCT	McInnes	0.43	0.19	0.98	0.04
	Withdrawals	RCT	Mogensen	0.97	0.13	7.04	0.98
	Withdrawals	RCT	Scram	2.66	0.35	20.30	0.34
	Withdrawals	RCT	Elliot	1.00	0.06	16.03	1.00
	Withdrawals	RCT	Koylan	0.11	0.05	0.25	0.00
	Withdrawals	RCT	Coca	0.69	0.12	4.05	0.68
	Withdrawals	RCT	Mimran	2.88	0.40	20.73	0.29
	Withdrawals	RCT	Mallion	0.99	0.32	3.05	0.99
	Withdrawals	RCT	Roca-Cusachs	0.44	0.15	1.27	0.13
	Withdrawals	RCT	Derosa #4470	0.11	0.01	1.15	0.07
	Withdrawals	RCT	Lacourciere	1.94	0.20	19.03	0.57
	Withdrawals	RCT	Shand	0.13	0.00	6.37	0.30
	Withdrawals	RCT	Tikkanen	0.44	0.18	1.08	0.07
	Withdrawals	RCT	Townsend	0.76	0.31	1.85	0.54
	Withdrawals	RCT	Neutel	0.08	0.02	0.32	0.00
	Withdrawals	RCT	Amerena	0.49	0.16	1.55	0.23
	Withdrawals	RCT	Karlberg	0.66	0.30	1.47	0.31
	Withdrawals	RCT	Black	0.89	0.36	2.20	0.81
	Withdrawals	RCT	Malacco	0.41	0.20	0.83	0.01
	Withdrawals	RCT	Naidoo	0.98	0.20	4.93	0.98
Fixed		RCT		0.49	0.38	0.62	0.00
Random		RCT		0.51	0.36	0.73	0.00
Fixed		Overall		0.48	0.38	0.62	0.00
Random		Overall		0.50	0.36	0.70	0.00



Caveats and concerns in relation to these data include the fact that only one study was considered to be of good methodological quality. Also, there was significant heterogeneity in the reporting of withdrawal data. Many studies reported limited data on withdrawal rates. Moreover, only one trial analyzed data to assess variation in withdrawal rates by specific demographic subgroups.[64]

Adherence and Persistence

Nineteen papers describing 17 distinct studies reported at least some information on persistence or adherence.[20,21,24,27,29,31,35,37,56-58,60,66-72] Studies of adherence consisted of RCTs that assessed reported pill counts or subject dropout. Since subject dropout did not uniformly reflect adherence with medication (as opposed to adherence with the study protocol, for example), we focused on the seven studies that measured pill counts. Studies of persistence – whether patients remain on the initial ACEI or ARB – included two RCTs as well as eight longitudinal cohorts in which patients were followed in a real-world setting. While adherence and persistence were lower in cohort studies than in the randomized trials, the general conclusions from the two groups of studies were similar.

With the possible exception of the study by Koylan et al.,[57] adherence with ACEIs and ARBs was similar (Table 7). Moreover, adherence was high, above 97 percent in five of the seven studies assessed. All of the studies appeared to define adherence as the percentage of patients taking approximately 100 percent of the prescribed pills, although not every article was precise

in reporting how this figure was derived. The absolute magnitude of adherence depended on the width of the acceptable range (e.g., McInnes et al.[56] used a narrow range of 90 to 110 percent of prescribed pills, so might be expected to report lower adherence than Malmqvist et al.,[24] which considered a wider range of 75 to 125 percent of prescribed pills to be acceptable). Also, randomized trials, which engender such biases as motivated volunteers and a Hawthorne effect, will tend to overestimate adherence in comparison with usual practice. Nevertheless, the overall conclusion that adherence was good and similar between ACEIs and ARBs seems well supported.

Table 7. Studies of adherence with ACEIs and ARBs

Study	Adherence with ACEIs	Adherence with ARBs	Definition of adherence
Amerena et al.[60]	99%	99%	Pill counts at 6 weeks
	98%	98%	Pill counts at 12 weeks
Coca et al.[58]	98.4%	98.3%	Taking 80-110% of pills
Koylan et al.[57]	~94%	~96%	Taking pills daily at 1 month visit
	~86%	~96%	Taking pills daily at 3 month visit
	~87%	~96%	Taking pills daily at 6 month visit
Malmqvist et al.[24]	>98%	>98%	Taking 75-125% of pills at 6 weeks
	>98%	>98%	Taking 75-125% of pills at 12 weeks
McInnes et al.[56]	90%	90%	Taking 90-110% of pills
Rosei et al.[35]	98.2%	97.8%	Not specifically defined
Williams et al.[20]	>98.8%	>98.8%	Taking 80-120% of pills

Regarding persistence, the majority of evidence came from non-experimental studies, which are subject to a variety of caveats, described in detail below. These caveats notwithstanding, the results were quite consistent in that the persistence with ARBs was modestly better than the persistence with ACEIs (Table 8). Noting both the consistency of this finding across studies and the rather modest degree of differences in persistence, the conclusion that ARBs exhibit somewhat better persistence than ACEIs can be drawn with a moderate degree of confidence.

Table 8. Studies of persistence with ACEIs and ARBs

Study	Duration	ACEIs			ARBs		
		Continued	Switched	Discontinued	Continued	Switched	Discontinued
Randomized trials							
Saito et al.[37]	6 mo	71%	28%	2%	89%	9%	2%
Koylan et al.[57]	6 mo	~82%			~89%		
Longitudinal cohort studies							
Hasford et al.[29]		42%			44.7-60.8%		
Mazzaglia et al.[31]	1 yr	~50%	~8%	~42%	~50%	~10%	~40%

Study	Duration	ACEIs			ARBs		
		Continued	Switched	Discontinued	Continued	Switched	Discontinued
Bloom et al.[66]/Conlin et al.[68]	1 yr	58%	9%	33%	64%	7%	29%
	4 yr	46.5%	18.9%	34.6%	50.8%	16.5%	32.7%
Erkens et al.[71]	1 yr	59.7%			62.0%		
Marentette et al.[72]	1 yr			~35%			~15%
Bourgault et al.[67]	1 yr			41%			34%
	2 yr			53%			44%
	3 yr			60%			47%
Degli Esposti et al.[70]	1 yr	30.7%	9.4%	59.9%	33.4%	24.6%	42.0%

The results of the longitudinal studies should be considered in light of several caveats. The longitudinal cohort studies typically use administrative databases and, even though investigators control for differing patient characteristics as much as possible, this design cannot assure that patients receiving different medications are similar, even after statistical adjustment. Accordingly, the consistency of results across multiple studies is crucial. Results of multi-predictor analyses, when present, yield substantially similar conclusion to the simple comparison of unadjusted persistence provided above; accordingly, we focus on the unadjusted results.

The ideal outcome would disaggregate patients into four mutually exclusive and exhaustive categories: (1) continued initial medication without change; (2) continued initial medication but added another medication from a different class; (3) changed to another medication from a different class; and (4) discontinued medication entirely. Almost all of the reports aggregated the first two categories, which we have combined throughout. Within each category, definitions are not entirely consistent, but are close enough for purposes of comparison

As a final caveat, some of the studies (e.g., Marentette et al.,[72] Bourgault et al.,[67] and the study described in two papers by Degli Esposti et al.,[69,70] the latter of which could only be abstracted for qualitative information and is not discussed further) corresponded in time to the introduction of ARBs, and thus have small sample sizes for this class of medications. Accordingly, for these studies persistence is estimated with less precision than might be desired.

Key Question 3. Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?

Key Points

- Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs and ARBs for any particular patient subgroup.

Blood Pressure

We did not identify any subgroup of patients in which one ACEI or ARB was clearly superior. Two of 49 studies reporting blood pressure outcomes included only women,[24,43] and two additional studies reported results for a female subgroup.[22,59] Three of these four found no significant difference in blood pressure effects between the ACEI and the ARB treatment arms; however, the largest of these studies reported superior blood pressure lowering in the ARB arm compared to the ACEI (n = 286, mean between group difference 5.5/2.2 mm Hg; $p < 0.01$). There were three studies conducted exclusively in elderly patients (age $\geq$ 65), and three additional studies that reported separate results for this age group.[10,16,22,27,38,59] Four of these studies showed no difference between ACEI and ARB treatment in elderly patients, with two studies reporting better blood pressure lowering in the ARB arm. Seven studies were conducted only in diabetic patients with hypertension, none of which showed a difference between the two classes of medication.[15,17,19,32,35,41,42] In four of studies, blood pressure was reported as an outcome in a subgroup of black patients.[13,36,38,65] Three of these studies found no difference in the efficacy of ACEI or ARB in black patients, while one reported significantly better DBP lowering in ARB treated patients compared to ACEI.[38]

Mortality and Major Cardiovascular Events

Because of scant data on mortality, MI, and stroke, it was not possible to assess whether ACEIs and ARBs have any differential effect on event rates in any subgroups of patients based on demographic characteristics, use of other medications concurrently, or comorbidities.

Quality of Life

None of the included trials reported any differential impact of ACEIs versus ARBs on quality-of-life measures by clinically relevant subgroup.

Safety and Adverse Events

In general, there is no evidence supporting differential rates of adverse events for ACEIs versus ARBs with regard to any specific subgroup. However, one study included only women in the

study population.[24] The overall rates of cough reported by the study were similar to those reported by other studies that included men and women. One study reported results for a female subgroup.[64] The proportion of women in the latter study was 55.7 percent, and rates of cough in this study were higher for women treated with ACEIs (statistically significant for two of the three ACEIs studied in the trial) than they were for women treated with ARBs.

Adherence and Persistence

There is not sufficient evidence that particular patient subgroups are more or less likely to be persistent in taking either an ACEI or ARB. However, some observations emerge regarding persistence with either agent (Table 9). The most consistent result is that persistence increased with age: patients in the 65-to-84-year-old age range tended to exhibit the highest persistence of all. The contribution of sex was inconsistent. There is some evidence that a history of cardiovascular disease is associated with greater persistence, a possible explanation being that such a history could make hypertension management more salient to the patient.

Table 9. Predictors of persistence with ACEIs and ARBs

Study	Predictors of persistence
Mazzaglia et al.[31]	Increasing age, family history of cardiovascular diseases and diabetes, no severe hypertension, low chronic disease score
Bloom et al.[66] (1yr)/Conlin et al.[68] (4 yr)	1 yr: Increasing age, < 1 dose per day, male sex 4 yr: Increasing age, female sex
Erkens et al.[71]	Increasing age, male sex, antidiabetic drugs, lipid lowering drugs, previous cardiovascular hospitalizations
Marentette et al.[72]	Increasing age, female sex
Degli Esposti et al.[70] (1 yr)/Degli Esposti et al.[69] (3 yr)	1 yr: Increasing age, medications for heart disease or diabetes, previous cardiovascular hospitalizations, ≥ 2 comorbidities 3 yr: Increasing age, male sex, younger general practitioner, male sex of general practitioner

Lipids

Several potentially relevant subgroups were identified, but none had a clear difference in outcomes for lipid parameters. Six studies evaluated patients with diabetes.[15,17,19,32,41,42] These included three that found small changes in various lipid parameters,[17,19,41] but the other three found none.[15,32,42] Other populations studied – including postmenopausal women,[43] Asians,[39] and Turks[19] – did not have detectable changes in the lipid profile.

Diabetes Markers

In the six studies requiring diabetes as an inclusion criteria, four found no difference in individuals receiving ACEIs or ARBs in glucose or HgbA1c levels;[15,19,32,42] one found no change

in glucose but a small statistically significant increase in HgbA1c for the ARB (+0.25% enalapril, +0.6% losartan; data not reported for between-group comparisons);[17] and one found no change in HgbA1c but a decline in glucose levels for both which was statistically greater for the ACEI (perindopril -15 ± 4 mg/dL, candesartan -8 ± 2 mg/dL).[41] Thus, for the two studies for which a difference was found, the difference was discrepant (i.e., an increase in HgbA1c in one and a decline in glucose in the other), and only one directly analyzed differences between the two groups.

In addition to studies of individuals with diabetes, measures of glucose or HgbA1c were performed for several other subgroups including Asians,[39] Turks,[19] Brazilians,[45] and postmenopausal women.[43] None of these studies identified a difference in the impact of ACEIs and ARBs with regard to glucose or HgbA1c.

LV Mass/Function

Although five of the eight studies that presented results on LV mass or function demonstrated some decreases in LVMI, the sum of the evidence does not demonstrate a difference between ACEIs and ARBs with regard to their effect on LV mass or function for individuals with essential hypertension. No subgroup analyses were performed to help identify subgroups of patients who were more likely to have improvements in LV mass or function in any of the studies. However, all five of the studies that demonstrated some improvement from baseline to followup in LVMI[18,23,25,40,45] had a substantial prevalence of LVH among their patients (23 to 100 percent).

Two studies did suggest potential differences between ACEIs and ARBs; however, limited conclusions may be drawn from these studies because of several methodological concerns. The study by Avanza et al.[45] demonstrated lower reduction of LVMI among those treated with enalapril versus losartan (12.4 ± 3.2 percent versus 9.1 ± 2.1 percent, $p < 0.05$). However, this study was a poor-quality, non-randomized controlled trial that included only 15 patients in each group and had only moderate duration of followup (10 months). The other study, by Shibasaki et al.,[18] demonstrated lower reduction among those treated with losartan versus enalapril (24.7 ± 3.2 percent versus 11.2 ± 4.1 percent, $p = 0.026$). However, definitive conclusions from this study are limited because it was conducted in patients with end-stage renal disease, included only 10 patients in each group, and also had only moderate duration of followup (6 months). Notably, all patients in both of these contradictory studies had LVH at baseline.

GFR/Proteinuria

There are no consistently demonstrated differential effects with use of either ACEIs or ARBs related to either renal function (as measured by creatinine or GFR) or reduction of urinary protein or albumin excretion. As a result, we were not able to identify subgroups of patients for whom either ACEIs or ARBs are more effective in preserving renal function or decreasing urinary protein or albumin excretion, or are better tolerated without causing sustained elevations in serum creatinine.

Summary and Discussion

A succinct summary of the results of this review of the comparative long-term benefits and harms of ACEIs versus ARBs for adults with essential hypertension is provided in three tables. First, we give an aggregated view of the level of evidence and brief conclusions (Table 10). Second, we describe the nature and quality of the evidence in a format recommended by the GRADE Committee (Table 11). Finally, we summarize the quantitative analyses of outcomes, offering an estimate of the comparative outcomes for ACES (Table 12).

Table 10. Summary of evidence on comparative long-term benefits and harms of ACEIs vs. ARBs for hypertension

Key Question	Level of Evidence	Conclusion
1. Key Question 1. For adult patients with essential hypertension, how do ACEIs and ARBs differ in the following health outcomes:		
a. Blood pressure control?	Fair	ACEIs and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. This conclusion is based on evidence of generally moderate quality from 49 studies (45 RCTs, two non-randomized controlled clinical trials, and one retrospective cohort and case-control study) with a total of 16,347 patients followed for periods from 12 weeks to 3.3 years (median 16 weeks). There was a minimally higher rate of treatment success based on use of a single antihypertensive for ARBs compared to ACEIs (approximately 1 fewer patients per 100 treated with ARBs will require more than a single agent, number-needed-to-treat [NNT]). The advantage of ARBs for this outcome was heavily influenced by retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients, or RCTs with very loosely defined protocols for medication titration and switching.
b. Mortality and major cardiovascular events?	Poor	Due to insufficient numbers of deaths or major cardiovascular events in the included studies, it is not possible to discern any differential effect of ACEIs vs. ARBs for these critical outcomes. In eight studies that reported mortality, MI, or clinical stroke as outcomes, six deaths and one stroke were reported. This may reflect low event rates among otherwise healthy patients and relatively few studies with extended followup.
c. Quality of life?	Good	No differences were found in measures of general quality of life; this is based four studies, two of which did not provide quantitative data.

Key Question	Level of Evidence	Conclusion
d. Risk factor reduction and other intermediate outcomes?	Fair to good (with the exception of progression to type 2 diabetes mellitus, poor)	There were no consistent differential effects of ACEIs versus ARBs on several potentially important clinical outcomes including lipid levels, progression to type 2 diabetes mellitus, markers of carbohydrate metabolism/diabetes control, left ventricular mass or function, or progression of renal disease (either based on creatinine, glomerular filtration rate, or proteinuria). While based on studies of at least moderate quality, relatively few studies assessed these outcomes over the long-term.
2. Key Question 2. For adult patients with essential hypertension, how do ACEIs and ARBs differ in safety, adverse events, tolerability, persistence, and adherence?	Fair to good	ACEIs have been consistently shown to be associated with greater risk of cough than ARBs (pooled odds ratio = 0.34). For clinical trials, this translates to a difference in rates cough of 5.7 percent ((NNT = 18); however, for cohort studies with lower rates of cough, this translates to a difference of 1.3 percent (NNT = 76). This is consistent with evidence reviewed regarding withdrawals due to adverse events, in which the NNT is on the order of 64 – that is, one more withdrawal per 64 patients treated with an ACEI versus an ARB. There was no evidence of differences in rates of other specific adverse events.
3. Key Question 3. Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?	Poor to fair	Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs and ARBs for any particular patient subgroup.

Table 11. GRADE summary table

Studies	Design	Quality	Consistency	Directness	SD	SA	PB	DR	PC
Outcome: Blood pressure control									
49	RCTs	Confounded by additional treatments, dose escalation	Consistent results	Direct	-	-	-	-	-
Outcome: Mortality and major cardiovascular events									
8	RCTs	No serious limitations	Consistent results	Direct	+	-	-	-	-
Outcome: Morbidity/quality of life									
4	RCTs	No serious limitations	Consistent results	Direct	-	-	-	-	-
Outcome: Safety (serious and overall adverse events, withdrawals due to adverse events)									
23	RCT (1 non-randomized	Variation in study	Consistent	Direct	-	-	-	-	-

Studies	Design	Quality	Consistency	Directness	SD	SA	PB	DR	PC
	control trial; 1 case-control)	protocols and data reporting	results						
Outcome: Specific adverse events									
30	RCTs and 2 cohort studies	Variation in data reporting	Consistent results	Direct	-	-	-	-	-
Outcome: Persistence/adherence									
19	RCTs and 8 cohort studies	No serious flaws	Consistent results	Direct	-	-	-	-	-
Outcome: Rate of use of a single agent for blood pressure control									
22	RCTs (+ 3 observational studies)	No serious flaws	Consistent results	Direct	-	-	-	-	-
Outcome: Lipid levels									
12	RCTs (1 case-control)	No serious flaws	Inconsistent results between studies; between lipid parameters	Direct	-	-	-	-	-
Outcome: Rates of progression to type 2 diabetes									
0	NA	NA	NA	NA	+	-	-	-	-
Outcome: Markers of carbohydrate metabolism/diabetes control									
13	RCTs (2 observational studies)	No serious flaws	Inconsistent results between head-to-head studies and placebo-controlled studies	Direct	-	-	-	-	-
Outcome: Measures of LV mass/function									
8	RCTs (1 non-randomized control trial; 1 case-control)	Poor quality studies; small sample sizes	Consistent results	Direct	-	-	-	-	-
Outcome: Measures of kidney disease									
15 GFR	RCTs (except 3)	Poor quality studies; different parameters measured	Consistent results	Direct	-	-	-	-	-
9 protei-nuria			Inconsistent results	Direct	-	-	-	-	-

Abbreviations: DR = dose response; PB = publication bias; PC = all plausible confounders would reduce the effect; RCTs = randomized controlled trials; SA = strong association (+ = very strong, ++ = extremely strong); SD= sparse data

Table 12. GRADE balance sheet

Outcome	Number of patients		Effect based on pooling		Quality	Relative importance
	ACEI	ARB	Effect (95% CI)	NNT		
BP reduction	~ 8000	~ 8000	-	-	Moderate	Critical
Rate of use of a single antihypertensive for BP control	2668/7296 (37%)	2228/4714 (48%)	Risk difference 1% (0% to 3%)	100	High	
Mortality and major CV events	1702	1707	-	-	Moderate	Critical
Morbidity/QoL	~ 550	~ 550	No difference detected	-	Low	-
Cough	1091/42,029 (2.6%)	203/19,949 (1%)	Peto odds ratio 0.34 (0.30 to 0.39)	18 to 76*	High	
Adverse events – withdrawals	188/3488 (5.4%)	112/4001 (2.8%)	Peto odds ratio 0.50 (0.36 to 0.70)	64	High	Critical
Lipid levels	870	807	-	-	Moderate	-
Progression to type 2 diabetes	No data	No data	-	-	Low	-
Markers of carbohydrate metabolism/diabetes control	807	741	-	-	Moderate	-
Measures of LV mass/function	196	138	Effect size (SMD) 0.04 (-0.19 to 0.27)	-	High	-
Measures of kidney disease – GFR	226	169	Effect size (SMD) 0.08 (-0.13 to 0.29)	-	High	-
Measures of kidney disease – proteinuria	117	114	Effect size (SMD) -0.25 (-0.51 to 0.02)	-	Moderate	-

* The observed rates of cough appear much higher in RCTs than cohort studies; this is due to the higher detection when the patient is queried systematically for this symptom. Thus, based on the overall odds ratio of 0.341, when we use the rate of cough with ACEIs equal to the RCTs (8.9%) the absolute rate difference is estimated 5.7% (NNT = 18); however, when we use the rate of cough with ACEIs equal to the cohort studies (2%) the absolute rate difference is estimated to be 1.3% (NNT = 76). The latter estimate is likely to be more clinically relevant.

Abbreviations: BP = blood pressure; CI = confidence interval; CV = cardiovascular; GFR = glomerular filtration rate; LV = left ventricular; NNT = number-needed-to-treat; QoL = quality of life; SMD = standardized mean difference

Future Research

The hypothesis that ACEIs and ARBs have clinically meaningful differences in long-term outcomes in individuals with essential hypertension is not strongly supported by the available evidence. Further research in this area should consider:

- Subgroups of special importance such as individuals essential hypertension and diabetes mellitus, congestive heart failure, chronic kidney disease, and dyslipidemia.
- Pragmatic designs such as clinical trials in which treatment is consistent with typical clinical practice, or randomization by organizationally meaningful clusters, such as practice organizations or health plans.
- Outcomes over several years.
- Outcomes measured according to current clinical standards.
- Broader representation of groups such as the elderly and ethnic and racial minorities.

Given the demonstrated higher incidence of cough with ACEIs, it would be valuable to gain more precise understanding of the impact of cough on quality of life, care patterns (e.g., use of therapeutic agents for cough symptoms or conditions associated with cough), and health outcomes, particularly for individuals who continue to use ACEIs.

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Abbreviations

ACEI(s)	Angiotensin-converting enzyme inhibitor(s)
AHRQ	Agency for Healthcare Research and Quality
ARB(s)	Angiotensin II receptor antagonist(s)
CER	Comparative Effectiveness Review
DBP	Diastolic blood pressure
EF	Ejection fraction
EPC	Evidence-based Practice Centers
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HgbA1c	Glycated hemoglobin
HCTZ	Hydrochlorothiazide
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
MeSH	Medical Subject Headings
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SD	Standard deviation
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SRC	Scientific Resource Center
TC	Total cholesterol
TG	Triglyceride
UAE	Urinary albumin excretion
USPSTF	U.S. Preventive Services Task Force